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CONTENTS

PAGE

The Significance of Syphilis in Prenatal Care and in the Causation of Fœtal Death. By J. Whitridge Williams 141

Transient and Paroxysmal Auricular Fibrillation. (Illustrated.) By V. R. Mason 145

Presentation to the University of the Portrait of Dr. Florence Rena Sabin. (Illustrated.) 151

Determination of the Acidity of Gastric Contents. I. Determination and Significance of Acidity. (Illustrated.) By Alfred T. Shohl 152

PAGE

Determination of the Acidity of Gastric Contents. II. The Colorimetric Determination of Free Hydrochloric Acid. (Illustrated.) By Alfred T. Shohl and John H. King 158

Determination of the Acidity of Gastric Contents. III. Combined Acidity and Buffer Value. By Alfred T. Shohl and John H. King 162

Minute on the Death of Sir William Osler 166

Contributions to Psychopharmacology. By David I. Macht 167

A Biological Study of Hemolytic Streptococci from Throats of Patients Suffering from Scarlet Fever. Preliminary Report. By Walter P. Bliss 173

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THE SIGNIFICANCE OF SYPHILIS IN PRENATAL CARE AND IN THE CAUSATION OF FŒTAL DEATH[1]

By J. Whitridge Williams

I think that it may safely be said that the propaganda for the development and extension of prenatal care, which has been conducted during the past few years in this country, constitutes one of the most important advances in practical obstetrics; as it has taught us to appreciate the unnecessary wastage of fœtal life which has occurred in the past and to consider seriously how it may be diminished.

Unfortunately, this movement is not of medical origin, except in so far as the efforts of the pediatricians to popularize maternal suckling had led to some supervision over pregnant women. Years ago Budin instituted consultations for pregnant women in Paris, and Ballantyne of Edinburgh did important pioneer work concerning the production of fœtal abnormalities and insisted upon the benefits which might follow intelligent antenatal care, yet real interest in the prophylactic supervision of pregnant women originated with laymen. Indeed, I do not think that I shall go far wrong when I state that the greatest credit in this respect belongs to Mrs. William Lowell Putnam, who some years ago organized at her own expense in Boston a small service in which women could be supervised during the latter half of pregnancy for the purpose of instruction in the rudiments of the hygiene of pregnancy, of seeing that they were properly nourished and not overworked, of teaching the importance of suckling their children when born, and particularly of preventing the occurrence of eclampsia by the early recognition and treatment of the toxæmias of pregnancy.

One of the most important agencies in bringing about the reform in this country has been The Association for the Prevention of Infantile Mortality—now the American Child Hygiene Association; for at its meetings each year philanthropic laymen, social workers and trained nurses, as well as occasional medical men, read papers upon the subject and gradually aroused popular interest in it, and it was not until after the movement had attained considerable momentum that obstetricians became generally concerned with it, and even at present many of them still treat the subject in a luke-warm manner.

In its broadest sense, prenatal care may be defined as such supervision of the pregnant woman as will enable her to go through pregnancy safely, to bring forth a normal living child with minimal danger, and to be discharged in such good physical condition as to be able to care for her child

[1] Read before the Section on Obstetrics and Gynecology of the Medical Society of the state of New York, March 25, 1920.

efficiently and to suckle it for at least the first months of its life. This means that the women must be under medical supervision from the earliest possible period of pregnancy, so its various abnormalities may be recognized at their inception and treated prophylactically. It also means the application of the best methods of obstetrical diagnosis during the weeks immediately preceding labor, so that abnormal presentations, disproportion due to contracted pelves, as well as other complications may be recognized, and corrected if possible before its onset. It further means the proper conduct of labor, and such supervision during the weeks immediately following it, that the woman may be discharged in such physical condition as to be able to carry on her usual avocations efficiently, and to give her child the necessary care. Finally, it implies medical supervision of the child during the first year of life, so that the effort expended during pregnancy and at the time of labor be not wasted; as it should be realized that the object of pregnancy is to secure a child which will have a reasonable prospect of reaching adult life, and that every preventable fœtal or infantile death means biological and economic waste.

It is evident that such a program requires not only first-rate obstetrical care, but such supervision of the patient before and after delivery by trained nurses and social workers as will make it possible for her to realize the importance of following closely the various regulations laid down for her guidance. In other words, efficient prenatal care must be regarded in great part as a campaign of education for physician and patient, in which both must be taught to realize that ideal obstetrics implies not merely intelligent care at the time of labor, but that it has a much wider scope and should begin as soon as the woman realizes that she is pregnant and continue until she is discharged in ideal physical condition and suckling a normal child. As the majority of hospital patients belong to the less intelligent classes, it is only by means of education through prenatal workers that they can be induced to make the necessary visits to the dispensary before and after delivery, and consequently I have become convinced that efficient prenatal and postnatal care cannot be carried out by physicians alone, and is feasible only when the requisite number of trained nurses and social workers are available.

In the earlier work, attention was principally concentrated upon three points: (1) The recognition and earliest possible treatment of the toxæmias of pregnancy in the hope of preventing the development of eclampsia; (2) supervision of the general physical and material condition of the patient with the object of diminishing the chances of premature labor; and (3) such instruction during the latter part of pregnancy that the mother will be prepared to suckle her child after it is born. When, however, the subject was taken up by obstetricians, it became apparent that the best results could not be obtained unless the scope of the work were materially widened so as to include everything which is implied by good obstetrics, plus the supervision and instruction derived from nurses and social workers.

Soon after taking up this work, I realized that the recognition and treatment of syphilis early in pregnancy constituted an important and fruitful field for a radical reduction in fœtal mortality, and in my presidential address—"Upon the Limitations and Possibilities of Prenatal Care"—before the American Association for the Prevention of Infantile Mortality in 1915, I developed the idea that more lives could be saved along such lines than by any other single method. That address was based upon the critical study of 700 fœtal deaths occurring in 10,000 consecutive deliveries in the Obstetrical Service of The Johns Hopkins Hospital, and included not merely the deaths at the time of labor, but also those occurring during the last ten or twelve weeks of pregnancy, as well as those during the two weeks immediately following delivery. Upon analyzing the causes of death, it was found that syphilis was responsible for 26 per cent of the entire number, and that it caused more deaths than any other single factor, and very many more than the toxæmias of pregnancy, which up to that time had been considered the greatest field for prophylactic effort. Consequently, I concluded that if syphilis could be eliminated from among the causes of fœtal death, greater progress in prenatal care would be made than by any other means at present available.

In the 700 cases under consideration the diagnosis was made by the recognition of congenital syphilis in the living child, or from the presence of certain histological changes in the placenta which we had learned to associate with the disease, while in only a relatively small proportion of the cases was it made at autopsy. With the discovery of the Wassermann reaction and the demonstration that the spirochete is the cause of syphilis, our knowledge concerning the disease became greatly widened, so that we were able to diagnosticate it in many mothers and infants in whom it had formerly been overlooked, as well as to demonstrate the syphilitic nature of certain lesions which had previously not been considered as having any relation with that disease.

While preparing my article in 1915, I became convinced that the only way in which the problem could be approached with any hope of effective solution was by determining the Wassermann reaction in every pregnant woman who registered in the Dispensary, and subjecting her to intensive anti-syphilitic treatment whenever it was positive.

This work was begun in April, 1916, and the present paper is based upon the critical study of 302 fœtal deaths occurring in 4000 consecutive deliveries between that period and December 31, 1919. In this series every effort was made to elicit a possible history of syphilitic infection and to detect the presence of the clinical signs of the disease; moreover, a Wassermann test was made at the first visit of the patient, and, if a positive result were obtained, she was subjected to proper treatment in the Syphilis Clinic, provided sufficient time was available before delivery. At the conclusion of labor a Wassermann was likewise taken from the fœtal blood obtained from the maternal end of the umbilical cord. Every placenta was preserved and examined histologically, and finally, if the child was born dead or died after delivery, every effort was

made to obtain an autopsy in order to determine accurately the cause of death, particular attention being given to the recognition of syphilitic lesions and to the demonstration of the presence of spirochetes. Consequently, in each of these 4000 cases we have a careful clinical history of the patient, as well as a record of the maternal Wassermann, of the fœtal Wassermann at the time of birth, of the microscopical examination of the placenta, and in case of death of the child a complete autopsy, so that it is apparent that few cases of syphilis could escape recognition. Furthermore, all patients who presented a positive Wassermann were followed up by our social workers, and every effort was made to see that they were appropriately treated. At present we are endeavoring to get back as many patients as possible, who at any time presented signs of syphilis, for the purpose of ascertaining what has happened to them and their children. Unfortunately, however, this information will not be available for incorporation into this paper, which is based more particularly upon the critical study of the fœtal deaths occurring in this series of cases, while the conclusions to be drawn from the Wassermann reaction will be considered in a report to be made to the American Gynecological Society in May.

I think it only fair to preface our study by saying that our material differs from that which may be collected in many other cities by the fact that somewhat more than one-half of our patients were blacks. Thus, in the 4000 cases under consideration, there were 1839 white and 2161 black women, in whom a positive Wassermann reaction was present in 2.48 and 16.29 per cent, respectively. In other words once in every fortieth white, and once in every sixth colored woman. It should, however, be borne in mind that this incidence does not exhaust the possibilities of syphilis, as there were 105 additional women in the series in whom the Wassermann reaction was negative, but in whose histories some mention was made of syphilis. Forty-four of these had presented a positive Wassermann in a previous pregnancy, which had later become negative following efficient treatment, with the result that the present pregnancy ended in the birth of a normal child. On the other hand, in the remaining 61 women, autopsy revealed characteristic lesions and the presence of spirochetes in the fœtal tissues, or the live child presented clinical evidence of hereditary syphilis, or the placenta showed characteristic histological lesions.

Of the 302 dead babies 212 came to autopsy. In the former are included not only those dying at the time of labor or during the two weeks immediately following it, but also those dying during pregnancy from the time of viability onward: namely, children weighing between 1500 and 2500 grammes or measuring between 35 and 45 cm. in length. Of the 302 deaths, 99 occurred in white and 203 in black infants, an incidence of 5.4 and 9.4 per cent, respectively; while 157 occurred at the time of labor or during the first two weeks of the puerperium, and 145 were in premature children.

Syphilis was noted in 104 cases, in 89 of which the diagnosis was confirmed by autopsy with the demonstration of spirochetes in the fœtal tissues; while in the remainder it was made from the presence of syphilitic lesions in the placenta, associated with a positive Wassermann on the part of the mother. Upon analyzing the causes of death, we obtained the following figures:

	Cases	Percentage
Syphilis	104	34.44
Dystocia	46	15.20
Toxæmia	35	11.55
Prematurity	32	10.59
Cause unknown	26	8.61
Placenta prævia and premature separation	16	5.28
Deformity	11	3.64
Eleven other causes	32	10.69
	302	100.00

Before considering these figures critically, it may be well to say a few words as to how the classification was established, it being understood that the cause of death was determined partly from the autopsy findings and partly from careful study of the clinical history of each case. Thus, in 89 of the 104 syphilitic cases, the cause of death was determined by autopsy, while in the remaining 15 it was based upon clinical findings in the child, or upon the presence of syphilitic lesions in the placenta associated with a positive maternal Wassermann.

Under dystocia are included all deaths resulting from mechanical difficulty or undue delay at the time of labor; as for example, craniotomy, decapitation, birth injuries following operative delivery, prolapse of the cord, undue delay during the second stage incident to disproportion between the size of the child and the pelvis, etc. A certain proportion of such deaths must be attributed to error in judgment on the part of those conducting the delivery, while others were unavoidable. Under the deaths attributed to toxæmia are included not only the children which were born dead during an eclamptic attack, but also the premature live children, which were born spontaneously, or as the result of the induction of labor, and could not be raised.

In the category of prematurity, we have included only children whose imperfect state of development appeared to be the sole cause of death. In such cases, no lesions were found at autopsy, and the children appeared to be normal except for their small size. Of course it is possible that a more intensive search for spirochetes might have led to a positive result in a certain number of these cases, particularly when the maternal Wassermann was positive, but, as they were not found, the cause of death was set down as prematurity. Moreover, it should be understood that we have not included in this category premature children born of mothers suffering from toxæmia, placenta prævia or acute infectious diseases, etc., as under such circumstances death was attributed to the underlying disease, and not to the imperfect development of the child.

Great interest attaches to the 26 cases for which no cause of death could be ascertained. In none of the 14 babies included in this group which came to autopsy could definite

lesions be demonstrated; while in the other 12 careful study of the clinical course of labor did not enable us to formulate a satisfactory explanation for the fatal outcome. In several of the autopsy cases, syphilitic lesions could not be demonstrated in the fœtal organs nor spirochetes be found, despite the fact that the mothers presented a positive Wassermann or the placenta showed specific changes, so that death could not be attributed to syphilis, no matter what the presumption might be. This group of deaths is of great interest as it affords striking evidence of how little we really know of antenatal pathology, and suggests important possibilities for future research.

It is not necessary to consider in any detail the deaths associated with placenta prævia or with premature separation of the normally implanted placenta, as they are clearly the result of the underlying abnormality. Likewise, in the category of deformity, which includes examples of hydrocephalus, anencephalus, spina bifida, atresia of the intestinal tract, developmental abnormalities of the heart, etc., the condition originated in the earliest periods of embryonic life, and could not have been prevented by any means at our disposal.

Finally, in the last group are collected 32 deaths, which were attributable to one of eleven different causes, including atalectasis, about which we know nothing, acute infectious diseases of the mother, accidental suffocation, fœtal bacteræmia, hæmorrhagic disease, etc. Many of these were clearly unpreventable, while in others our knowledge concerning the underlying cause is so hazy as to make any positive statement inadvisable.

Upon analyzing the figures in the summary given above, it is seen that 89.3 per cent of the deaths are attributable to seven groups of causes, of which syphilis is the most important, as it accounts for 34.44 per cent of the total number, which is almost as high as the mortality for the next three groups combined, as dystocia, toxæmia and prematurity were responsible for 37.34 per cent, or only 3 per cent more than syphilis. Consequently, it is apparent that if it were possible to eradicate syphilis from our material, we should effect as great a reduction in fœtal mortality as by doing away with all fœtal deaths due to the various accidents at the time of labor, toxæmia, and prematurity combined. This, however, is manifestly out of the question.

As large as these figures seem, they do not entirely represent the ravages of syphilis, since we have already pointed out that it is quite possible that more careful search might have revealed the presence of spirochetes in the tissues of a considerable fraction of the autopsies in which the cause of death was attributed to prematurity, as well as in a certain number included in the unknown group. Moreover, these figures do not include the cases of congenital syphilis which appeared in babies which were discharged alive, or in whom the disease developed later.

It must be admitted that this unusually large incidence of syphilis can only apply to hospital services with a large black clientele, such as ours, and will not be noted in private practice or in hospitals in communities in which the majority of the inhabitants are white, or in which the colored people are more intelligent than here. Nevertheless, even if we consider only our white patients, syphilis still continues to be a very important cause of fœtal death, and this we know by experience can be in great part eliminated. As was indicated above, there were 99 white and 203 black infant deaths in our material, and in them syphilis was the etiological factor in 12.12 and 45.23 per cent, respectively. In other words, one out of every eight of our white babies died from syphilis as compared with every other black baby.

Upon comparing this 12 per cent mortality from syphilis in white infants with the other causes of death, it is seen that it exceeds all other causes except dystocia, and is nearly as great as for that. In other words, while 15.2 per cent of our children died from the various accidents of labor, 12.12 per cent of the white children died from syphilis, so that it is apparent that even in the white race syphilis represents one of the most important causes of fœtal death, and is responsible for a greater mortality than toxæmia. Consequently, we should avail ourselves of every method to recognize its existence as early as possible, and then to treat it energetically.

This means that all obstetrical patients should be encouraged to register not later than the third or fourth month of pregnancy, that a routine Wassermann should be made at the first visit, and in case the result is positive, intensive treatment should be started immediately. In the case of the ignorant patient, mere advice to return at stated dates for treatment will not suffice, and it will be necessary for the social worker to follow her to her home and insist upon the necessity of following all directions implicitly. This frequently requires numerous visits, but only in this way can ideal results be obtained. Of course this means the expenditure of a large amount of time on the part of the workers, as well as a considerable financial outlay.

I had hoped to be able to give figures showing a marked contrast between the results obtained in the past when the Wassermann was made only when indicated by the history of the patient and those obtained in the present series in which it constituted a routine procedure. Unfortunately, so many elements enter into such a comparison that the tabulations are not convincing, but the following figures will give a graphic idea of what may be accomplished. Of the 4000 women under consideration, 421 presented a positive Wassermann reaction, but unfortunately all of them did not receive ideal treatment. In many instances they registered too late to receive any treatment, while others returned so irregularly that they were imperfectly treated, as for some time we had too few prenatal workers to supervise the patients efficiently, with the result that only a relatively small proportion received ideal treatment. With this in mind, we have divided the 421 patients into three groups, namely:

a. No treatment.

b. Inefficient treatment. The patients who received only two or three injections of salvarsan and no after treatment.

c. Satisfactory treatment. The patients received from four to six injections of salvarsan followed by a course of mer-

curial treatment, with the result that the Wassermann became negative and remained so.

In the three categories there were 157, 103, and 163 patients, respectively, and the results of treatment are graphically showed by the fact that in group *a* 52 per cent of the children were born dead or presented some evidence of syphilis, as compared with 37 per cent in group *b*, and only 7.4 per cent in group *c*. In other words, the evidence at our disposal shows that if syphilis is recognized early in the pregnant woman, and is intensively and appropriately treated, almost ideal results may be obtained so far as the child is concerned. Consequently, there is every reason to hope that in the future syphilis may be practically eradicated as the cause of fœtal death in all properly conducted clinics in which the women register prior to the middle of pregnancy.

On the other hand, it must be realized that even with the most perfect mechanism, ideal results will never be obtained, inasmuch as our investigations show that the disease will escape recognition in a certain proportion of pregnant women for the reason that the women frequently exhibit no clinical manifestations and occasionally present a negative Wassermann as well, so that the existence of the disease is not suspected until a macerated child is born and is shown to be syphilitic at autopsy. This, however, should not discourage us, for such occurrences are comparatively rare, and if the course of procedure here outlined is faithfully followed, syphilis can be reduced from the most important cause of fœtal death to one of the least frequent.

I hope that you will not think I have been one-sided in presenting the subject as I have, or that my judgment has been warped by our experience in Baltimore. I am well aware that syphilis represents only one of the causes of fœtal death, and that all the others must be taken into consideration in a broad program for the reduction of fœtal mortality, but at the present time syphilis appears to offer the most promising field for immediate results. A little thought will make it clear that a considerable proportion of the deaths from dystocia are unavoidable, and until our knowledge concerning the mode of production of eclampsia has become further extended, we must consider that its prophylaxis has almost reached its limit. Likewise, there is no immediate prospect of reducing the mortality from prematurity, as we are almost entirely ignorant concerning the causation of spontaneous premature termination of pregnancy, except when syphilis, toxæmia or gross over-exertion is the underlying factor. Moreover, it must be acknowledged that the fœtal death-rate associated with placenta prævia and premature separation of the placenta is susceptible of only very gradual improvement while that due to congenital deformity is at present altogether beyond our control.

TRANSIENT AND PAROXYSMAL AURICULAR FIBRILLATION

By V. R. MASON

(From the Medical Clinic, The Johns Hopkins Hospital)

This paper will deal with the instances of transient and paroxysmal atrial fibrillation encountered at The Johns Hopkins Hospital since auricular fibrillation was first recognized. It does not include the instances of auricular flutter in which auricular fibrillation is often present for a variable length of time before the establishment of a normal rhythm, nor with the period of transition from a normal rhythm to permanent atrial fibrillation in mitral and other valve lesions and in cases of chronic myocarditis, unless this period occupied a considerable length of time.

The mechanism of atrial fibrillation was first suggested by Cushny [1] in 1899 and more definitely formulated by Cushny and Edmunds [2] a few years later. The work of Mackenzie,[3] Hering,[4] Lewis [5] and Rothberger and Winterberger [6] was, however, of fundamental importance. By means of polygraphic and electrocardiographic methods and animal experimentation, they were able to prove that Cushny's surmise was correct and to demonstrate the relative frequency and great importance of this arrhythmia in clinical medicine.

It is of interest that the patient, whose case was studied by Cushny and Edmunds [2] was subject to attacks of tachycardia with complete irregularity of the radial pulse over a long period of time and that this is probably the first instance of paroxysmal auricular fibrillation to be found in the literature.

Since then the recorded cases have increased somewhat in number, although no careful study of the condition has been made except by Krumbhaar [8] and by Heitz.[9] A number of other observers have reported a few isolated examples. Many of the reports, however, are incomplete, and in not a few lack of electrocardiographs or adequate polygraphic tracings makes it impossible to be certain of the exact nature of the arrhythmia.

It will be advantageous to summarize briefly some of the previous reports in an attempt to bring together certain evidence that has some bearing on the conclusions to be made below.

Hornung [10] in 1907 reported three instances of paroxysms of tachycardia with irregular radial rhythm in patients with hypertension and signs of myocardial insufficiency. Only radial pulse tracings are shown, but there can be little doubt but that he was dealing with arrhythmias dependent on paroxysms of auricular fibrillation.

A year later Hewlett [11] reported the case of a patient whom he had observed during eight paroxysms of atrial fibrillation. The patient was the subject of severe heart disease dependent on mitral stenosis.

Lewis [12] observed an instance of paroxysmal tachycardia in which the auricles fibrillated for about half a minute during one paroxysm. This patient had no obvious myocardial weakness. Four other cases are very briefly mentioned by him in a later report.[5]

Fox [13] reported the cases of Cushny and Edmunds [2] and Hewlett [14] and added two other cases. One patient was the subject of myocardial insufficiency in whom the irregularity later became permanently established; the other, a patient supposedly free from myocardial disease, developed a transient attack of atrial fibrillation following ether anæsthesia and a surgical operation.

Lewis and Schleiter [11] reported an interesting case of paroxysmal auricular fibrillation which they had observed for several months. During that time there were five paroxysms of atrial fibrillation, one of regular tachycardia and one attack in which both occurred. The patient had a mitral valve lesion and evidence of myocardial weakness. In another patient, an elderly man with arteriosclerosis and myocardial insufficiency, they observed many attacks of regular tachycardia and one attack of auricular fibrillation.

Heitz,[9] in a very complete article on the subject, reported 10 instances of paroxysmal auricular fibrillation. This group consisted mainly of elderly patients with hypertension and arteriosclerosis and consequent myocardial weakness. A few were the subjects of heart disease dependent on valvular lesions.

Robinson [15, 16] observed transient atrial fibrillation in a supposedly healthy man following hydrogen sulphide poisoning. The patient recovered completely. In another instance attacks of fibrillation occurred in a patient with cardiac hypertrophy, arteriosclerosis, and evidences of heart failure.

Fahrenkamp [17, 18] observed transient auricular fibrillation in the course of Basedow's disease, of pneumonia, and of fatal septicæmia, and also in a patient with myocardial weakness dependent on arteriosclerosis.

Cohn,[7] in a study of the behavior of the heart in 123 cases of acute lobar pneumonia, encountered 12 instances of transient auricular fibrillation.

Krumbhaar [6] observed transient atrial fibrillation, in the course of lobar pneumonia, in a patient with slight myocardial disease; also in a young man suffering from fatal cardiac decompensation during the course of a pericarditis and mitral valve disease.

Levine [19] in a series of 128 consecutive cases of atrial fibrillation at the Peter Bent Brigham Hospital found that in 14.1 per cent the arrhythmia was transient or paroxysmal. Details of these cases are not given. The series includes four cases of auricular flutter, two of acute rheumatic fever, three of chronic myocarditis and one each of pneumonia, hyperthyroidism, cancer of the œsophagus, chronic alcoholism and chronic valvular disease. In four other cases he thought the attacks followed active digitalis therapy and in one the condition followed a surgical operation under ether anæsthesia.

Weiser [20] reported the case of a patient with extensive endocarditic lesions in whom attacks of fibrillation had occurred.

There are probably more cases recorded in the literature, although a careful search has been made. Enough have been cited, however, to show, in general, the type of case in which the arrhythmia has been observed most frequently, as well as some of the rarer conditions under which it has been encountered.

Incidence.—The 18 cases which form the basis of this report were found among the hospital records of 258 medical admissions, classified under the heading "Auricular Fibrillation." Without deducting readmissions, in about 7 per cent of the total number of cases of auricular fibrillation the arrhythmia was transient or paroxysmal. This percentage is probably too low, for in some instances an arrhythmia which occurred for a few hours was not carefully analyzed; in other instances, even though the arrhythmia was due to fibrillation, it was not so classified among the hospital records.

This figure, however, agrees very closely with Krumbhaar's [6] statistics, but is considerably lower than the 14 per cent reported by Levine,[19] although the fact that he included several cases of auricular flutter in his series partly accounts for the higher percentage. Fahrenkamp's [18] figures are much smaller. In his opinion transient or paroxysmal atrial fibrillation is a very rare condition which is often confused with extrasystolic irregularities.

There are, however, enough well-studied cases in this series to prove that fleeting attacks of auricular fibrillation are not uncommon; indeed, it is probable that many of the attacks of palpitation and breathlessness of which elderly patients complain are due really to paroxysmal atrial fibrillation.

Definition of Terms.—The terms "paroxysmal" and "transient," as applied to auricular fibrillation, have been used synonymously in the literature, except by Krumbhaar.[6] He drew attention to a group of cases in which the attacks of fibrillation may be truly characterized as "paroxysmal" and some further proof of this assumption will be brought forward in this paper.

Auricular fibrillation, once it makes its appearance, is usually permanent. There are a few patients, however, in whom the transition from normal rhythm to permanent auricular fibrillation may not be abrupt, but may extend over several months. In such instances, attacks of fibrillation alternate with a normal cardiac rhythm throughout the transition period.

Many of the reported instances of transient and paroxysmal auricular fibrillation have occurred in patients in whom this transition period, for reasons that we do not understand, has been unduly prolonged, and it is possible that in every instance the arrhythmia would have become permanent had the patient lived long enough or been observed over a sufficient period of time.

Such reasoning, however, is largely a question of terms and does not disprove the assumption that there is a group of cases, clinically very similar and true to type, in which the arrhythmia, presumably due to auricular fibrillation, may occur in paroxysms throughout a period of 10 or even 20 years, and in which no evidence of a tendency of the arrhyth-

mia to become established permanently is present during the life of the patient or during the period of observation.

These instances present the picture of true paroxysmal auricular fibrillation, even though permanent auricular fibrillation occasionally occurs during the end stage, when symptoms of grave myocardial insufficiency present themselves. A full discussion of this clinical syndrome will be found below.

Transient auricular fibrillation is a much rarer condition. It has been observed most frequently during the course of acute intoxications and infections, and is caused by the action of such poisons on some part of the cardiac mechanism.

Association with Other Arrhythmias.—It is of interest that paroxysms of auricular fibrillation, of short duration, have been observed by Lewis [22] and by Lewis and Schleiter [11]

TABLE I

Case No.	Age	Size of heart	Symptoms of heart disease	Primary condition
1	66	Enlarged	Marked	Arteriosclerosis.
2	37	Enlarged	Marked	Mitral valve disease.
3	56	Enlarged	None.....	Exophthalmic goitre.
4	38	Enlarged	Marked	Arteriosclerosis. Hypertension.
5	64	Enlarged	None.....	Malignant endocarditis.
6	60	Enlarged	Slight	Chronic myocarditis.
7	52	Enlarged	Doubtful	Bronchopneumonia, mild. Chronic myocarditis.
8	66	Enlarged	Severe	Hypertension. Arteriosclerosis.
9	50	?	?	Bronchiectasis. Pleural effusion.
10	55	Enlarged	Marked	Aortic insufficiency. Arteriosclerosis.
11	67	Enlarged	Moderate	Hypertension.
12	32	Enlarged	Marked	Valvular disease.
13	42	Enlarged	Severe	Luetic pulmonary arteritis. Arteriosclerosis.
14	39	Enlarged	Severe	Acute and chronic endocarditis.
15	68	Normal	None.....	Hypertension. Carcinoma of œsophagus.
16	50	Normal	Slight	Hypertension.
17	55	Enlarged	Marked	Chronic nephritis. Hypertension.
18	58	Normal	Slight	Chronic myocarditis.

during the course of paroxysmal tachycardia of auricular origin. The relation of the two disturbances to each other is not clear. Both, however, are associated with abnormal auricular activity (see Figs. 10 and 2).

In one case observed by us (J. H. H.) paroxysms of regular tachycardia preceded paroxysms of auricular fibrillation (the electrocardiograms did not show auricular flutter). Eventually auricular fibrillation became permanent.

Falconer and Dean [21] and Schwartzmann [23] observed paroxysms of auricular fibrillation in patients with heart-block. Such instances are very rare and are probably purely coincidental.

Auricular flutter with paroxysms of auricular fibrillation has been observed frequently. Indeed, it is the rule for auricular flutter to be followed by auricular fibrillation for a longer or shorter interval before the inception of a normal rhythm.

Etiology.—Table I shows the age, the presence or absence of cardiac enlargement and cardiac symptoms and the probable etiological factors in the cases summarized below.

It is evident that over two-thirds of the patients were in the sixth decade and this has been true of most of the reported cases. The exceptions have occurred most frequently either in patients with severe endocardial lesions in whom the arrhythmia was dependent on a rapidly failing myocardium, or during the course of a pneumonia, sepsis or other acute intoxication.

The primary condition, of which auricular fibrillation, whether permanent, transient or paroxysmal, is a clinical sign, is not fully known at present. It is justifiable, however, to assume that in the great majority of instances myocardial lesions are present, although it is not impossible that the arrhythmia, in some cases, may be dependent on extracardiac factors. Gossage and Hicks [25] and Levine [10] have suggested that fibrillation may occur occasionally in normal hearts, and Robinson,[26] in a heart carefully studied after death, found no lesion to account for the arrhythmia.

In this series of cases, cardiac disease, as evidenced by symptoms of myocardial weakness with or without cardiac enlargement, has been a nearly constant finding as will be seen in Table I. In a few instances, in which the only evidence of cardiac disease was an attack of auricular fibrillation, it has been necessary to assume that cardiac changes due to arteriosclerosis or hypertensive vascular disease were present.

Transient auricular fibrillation has been observed but rarely among our cases. In two instances, Cases 5 and 9, acute infections precipitated the attacks. In Case 3 hyperthyroidism of long duration was present and had probably led to permanent cardiac damage.

We may group these 18 cases as follows:

A. Myocardial weakness due to hypertension, arteriosclerosis, chronic valvular lesions or unknown factors (Cases 1, 2, 4, 6, 7, 8, 10, 11, 12, 13, 14, 15, 17, 18).

B. Acute infections or intoxications (Cases 3 (?), 5, 9).

The cases of true paroxysmal auricular fibrillation are found in Group A; of transient auricular fibrillation in Group B.

Clinical Considerations.—There is a large group of cases presenting a fairly typical and uniform clinical picture in which the attacks of auricular fibrillation, recurring at intervals throughout many years, are the most striking clinical findings.

The patient is usually an elderly individual, whose symptoms consist of breathlessness and palpitation occurring in paroxysms, either during physical exertion, mental strain or at times even during sleep. Between the attacks there are relatively few symptoms referable to the cardiovascular system, although usually any unaccustomed exertion is followed by slight dyspnœa.

The patient seeks advice of a physician either on account of the "heart attacks" or because of increased breathlessness on exertion. Physical examination usually reveals the presence of increased cardiac dulness, some peripheral arteriosclerosis and occasionally hypertension. Subsidiary findings,

such as chronic bronchitis and emphysema or a mild grade of renal disease, may be present.

Electrocardiographic studies show a normal sequence except during an attack when either a coarse or fine type of auricular fibrillation is present.

Cases 1, 6, 10, 15, 16, 18 represent fairly typical instances of paroxysmal auricular fibrillation and demonstrate the similarity of symptomatology presented by this group of patients.

One is impressed by the fact that the clinical picture is that of mild or, of course, eventually, of more severe myocardial weakness in which the paroxysms of auricular fibrillation are prone to occur after any unusual demand on the heart.

Transient auricular fibrillation needs no special comment at this time. As stated previously, it is a rare condition due to the action of certain poisons on the heart-muscle, or perhaps on the nervous mechanism of the heart. The subject has been fully discussed by Robinson. Until the essential cause of auricular fibrillation is known the pathological condition necessary for its production will remain the subject of speculation.

A few patients with endocardial lesions have shown attacks of atrial fibrillation. In them the arrhythmia is one more sign of myocardial insufficiency and usually becomes permanent long before death. Such patients, in the majority of instances, are simply passing through a prolonged transition period.

Prognosis.—It is not possible to make any definite statement concerning prognosis until the essential cause of auricular fibrillation is known and the nature of the lesions which may lead to its inception is better understood.

A careful consideration of the instances of transient and paroxysmal fibrillation, however, demonstrates that, as a rule, there is either chronic progressive myocardial weakness or that the arrhythmia, in some unknown manner, is dependent on an intoxication or an infection.

In the latter instances complete recovery with resumption of normal rhythm often occurs.

The prognosis, in the group of cases to which the term paroxysmal fibrillation has been applied, depends on the extent and character of the underlying lesion.

In many instances very few signs and symptoms of myocardial disease are present, and in spite of frequent attacks of fibrillation such patients often live for many years, comparatively free from symptoms. In other instances, the myocardial disease may progress rapidly and lead to an early death.

Early operation in patients with hyperthyroidism and transient fibrillation might be followed by the resumption of normal rhythm, but as yet too few instances have been reported to permit definite statements.

Summary.—Eighteen cases of paroxysmal and transient auricular fibrillation are reported.

A certain proportion of these present a fairly typical clinical syndrome in which the attacks of auricular fibrillation are paroxysmal in character.

Case 1.—*Summary:* Paroxysmal fibrillation in association with arteriosclerosis and progressive myocardial weakness.

J. H., Med. No. 32493, aged 66. *Diagnosis:* Arteriosclerosis. Chronic myocarditis.

During past six months there have been increasing weakness, shortness of breath and 40 pounds loss of weight. On admission on April 27, 1914, there were signs of heart failure: large heart, B. P. of 150 systolic. Arteriosclerosis. Pulse irregular in force and rhythm. April 28, E. K. showed paroxysmal auricular fibrillation.

By May 5 the pulse was regular and remained so until discharge on May 22, 1914.

Case 2.—*Summary:* Transient auricular fibrillation in patient with severe cardiac disease following acute rheumatic fever and hyperthyroidism.

I. M., Med. No. 33625, aged 37. *Diagnosis:* Mitral stenosis and insufficiency. Adherent pericardium. Exophthalmic goitre.

The patient had had chorea at 12 and polyarthritis at 13 and 36. Since the last attack she had had dyspnœa and palpitation on exertion. There had been some œdema. On admission, January 21, 1915, she had a huge heart with mitral valve disease and suggestive signs of adherent pericardium. There were definite signs of hyperthyroidism.

January 22. Pulse absolutely irregular, confirmed by polygraphic tracings.

January 24. E. K. Shows L. V. extra systoles and normal "p" waves.

February 10. E. K. Atrial fibrillation.

February 17. E. K. Normal rhythm.

March 1. E. K. Auricular fibrillation, right and left ventricular extra systoles.

Case 3.—*Summary:* Numerous attacks of auricular fibrillation over many years; associated with chronic myocarditis. No symptoms of heart disease. Exophthalmic goitre.

L. M. S., Med. No. 34040, aged 56. *Diagnosis:* Exophthalmic goitre. Tumor of lung.

For the past 20 years the patient has had attacks of palpitation with rapid pulse at varying intervals lasting a few hours. Last June (1914) during a six-hour attack, the pulse was 170. In March, 1915, there were three brief attacks. On admission, April 14, 1915, there were no cardiac symptoms. Wide retromanubrial dulness. Cardiac dulness 15 by 3.5 cm. Huge goitre. Pulse regular in force and rhythm.

May 9, 1915. Attack of auricular fibrillation, confirmed by E. K. Duration 12 hours. Pulse rate 160-170 per minute.

May 11. Short attack.

June 1. Short attack.

Case 4.—*Summary:* Transient atrial fibrillation in a patient with severe nephritis, hypertension and myocardial disease.

M. B., Med. No. 35228, aged 38. *Diagnosis:* Chronic nephritis. Hypertension. Myocardial insufficiency.

About two months before admission began to have nycturia, headache, shortness of breath and œdema.

On admission on December 17, 1915, the patient was orthopnœic with œdema of the face and body. B. P. 165/85. Cardiac dulness 5 by 20 cm. Pulse regular. The urine showed a large amount of albumin.

At 9 p. m. the auricles began to fibrillate, but the pulse was regular the next day.

December 20, 1915. Another attack of auricular fibrillation, but the pulse was regular on December 23, 1915, and remained so until discharge on January 22, 1916.

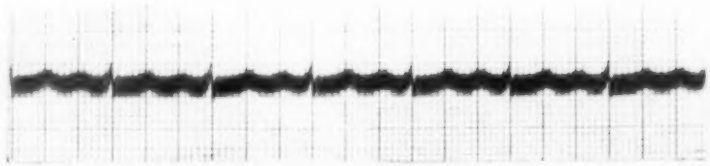

FIG. 1.—Case 14. L_2. Jan. 22, 1919.
Normal mechanism with sinus tachycardia.

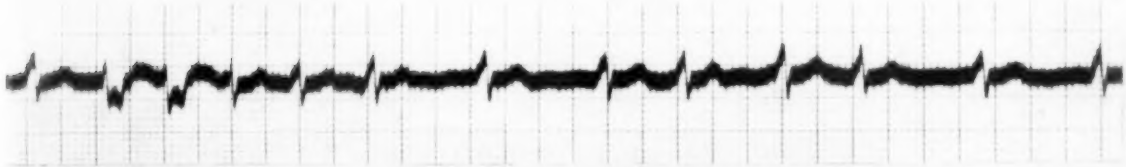

FIG. 2.—Case 14. L_2. Feb. 6, 1919.
Atrial fibrillation alternating with paroxysmal tachycardia.

FIG. 3.—Case 14. L_2. Feb. 6, 1919.
Paroxysmal tachycardia.

FIG. 4.—Case 16. L_2. June 19, 1919.
Paroxysmal auricular fibrillation.

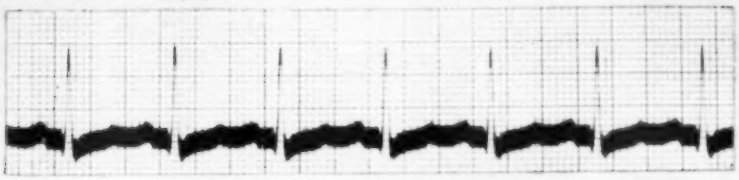

FIG. 5.—Case 16. L_2. June 20, 1919.
Normal mechanism.

FIG. 6.—Case 11. L_2. Nov. 18, 1918.
Auricular fibrillation.

FIG. 7.—Case 11. L_2. Nov. 26, 1918.
Slight sinus arrhythmia. Spaced "p" waves present.

FIG. 8.—Case 13. L_3. Jan. 28, 1919.
Normal mechanism.

FIG. 9.—Case 13. L_3. Jan. 30, 1919.
Paroxysmal tachycardia.

FIG. 10.—Case 13. L_3. Jan. 31, 1919.
Paroxysmal tachycardia alternating with atrial fibrillation.

FIG. 11.—Case 12. L_1. Nov. 9, 1918
Complete A. V. dissociation due to digitalis.

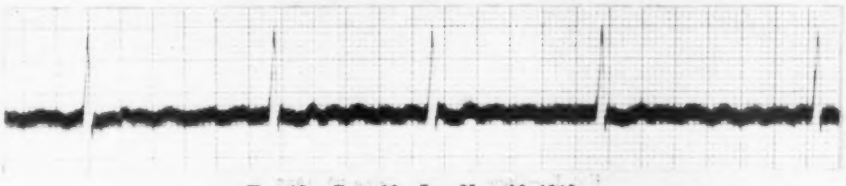

FIG. 12.—Case 12. L_2. Nov. 13, 1918.
Atrial fibrillation.

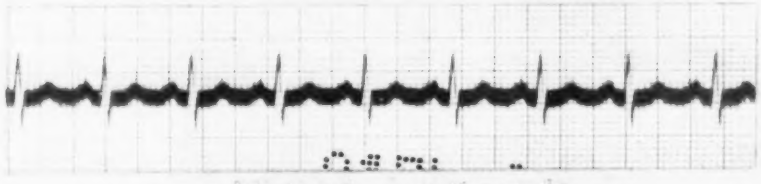

FIG. 13.—Case 12. L_2. Nov. 20, 1918.
Normal mechanism.

FIG. 14.—Case 12. L_2. Jan. 22, 1919.
Normal mechanism.

CASE 5.—*Summary:* Transient auricular fibrillation during course of malignant endocarditis.

J. C. B., Med. No. 37218, aged 64. *Diagnosis:* Mitral insufficiency. Bacterial endocarditis.

For the past six months there have been fever and progressive weakness.

On admission there was anæmia and weakness. Signs of mitral insufficiency. Large heart. *Streptococcus viridans* in blood and fever. Pulse regular in force and rhythm. During stay in hospital there were two short attacks of auricular fibrillation accompanied by palpitation and dyspnœa. The patient died several months later—January, 1917.

CASE 6.—*Summary:* Attacks of atrial fibrillation associated with mild myocardial insufficiency.

A. E. S., Med. No. 38851, aged 60. *Diagnosis:* Chronic myocarditis.

For the past two years has had attacks of marked palpitation lasting a few hours.

On admission on November 21, 1917, the pulse was totally irregular. B. P. 140/90. Cardiac dulness 3.5 by 14 cm. No marked symptoms.

November 22. E. K. Atrial fibrillation.

November 26, 27. E. K. Normal rhythm.

Discharged on December 17, 1917. Rhythm regular.

CASE 7.—*Summary:* Attacks of fibrillation of the auricles during the course of an acute bronchopneumonia in a patient with signs of slight myocardial disease.

H. T. B., Med. No. 39438, aged 52. *Diagnosis:* Chronic myocarditis. Bronchopneumonia.

Present illness began with cough, fever and pain in right side February 17, 1918.

On admission on February 19, 1918, there were signs of a mild bronchopneumonia. Cardiac dulness measured 4.5 by 14.5 cm. B. P. 130/80. Pulse totally irregular. E. K. shows atrial fibrillation.

February 20, the rhythm was normal, but attacks of fibrillation occurred on February 21 and on March 30, 1918.

Patient discharged on April 8, 1918. Normal rhythm.

CASE 8.—*Summary:* Transient attacks of atrial fibrillation during course of fatal heart failure secondary to arteriosclerosis and hypertension.

S. D., Med. No. 40095, aged 66. *Diagnosis:* Hypertension. Chronic myocarditis.

About December, 1917, the patient began to have dyspnœa on exertion. There has been progressive weakness. Œdema of legs for the past week. Admitted on July 16, 1918, with marked orthopnœa and some œdema. Peripheral vessels sclerosed. B. P. 195/140. Cardiac dulness measures 5 by 12 cm. Radial pulse regular. On July 17 auricular fibrillation set in, but the heart's rhythm was normal two days later. On July 23 the presence of auricular fibrillation was again shown by electrocardiograms, but soon disappeared. From this time until death—August 2, 1918—the pulse was regular in rhythm and numerous E. K.'s showed normal rhythm. *Autopsy:* Generalized arteriosclerosis, and more especially of renal arterioles. Cardiac hypertrophy.

CASE 9.—*Summary:* Attack of atrial fibrillation in patient with chronic pulmonary disease and probably myocardial weakness.

C. A. S., Med. No. 40293, aged 50. *Diagnosis:* Bronchiectasis. Pleural effusion.

About 18 months before admission the patient developed a cough with abundant sputum.

On admission on August 4, 1918, the pulse was regular in force and rhythm. The cardiac dulness was 15 cm. to the left and obscured on the right by a large pleural effusion.

On August 25 auricular fibrillation set in, but had disappeared the next day.

CASE 10.—*Summary:* Transient attack of atrial fibrillation in a patient with chronic myocardial insufficiency and aortic insufficiency dependent on arteriosclerosis (?).

J. B., Med. No. 40331, aged 55. *Diagnosis:* Myocardial insufficiency. Aortic insufficiency.

Signs of myocardial weakness for four years. An invalid for the past six months.

On admission August 24, 1918, there were dyspnœa and œdema. Cardiac dulness 4 by 16 cm. Well-marked aortic insufficiency. Pulse 100. Heart's rhythm normal.

August 27, 1918. Atrial fibrillation was present.

September 11, 1918. The electrocardiogram showed a normal rhythm.

The patient left hospital much improved, the blood-pressure had fallen from 190/100 to 140/80.

CASE 11.—*Summary:* Transient atrial fibrillation associated with severe myocardial disease and hypertension.

M. M., Med. No. 40868, aged 67. (Figs. 6 and 7.) *Diagnosis:* Hypertension. Chronic myocarditis.

For 15 years there has been palpitation on exertion. In September, 1918, the pulse was absolutely irregular.

On admission on November 15, 1918, there were symptoms of heart failure. The radial pulse was totally irregular. The blood-pressure was elevated. Cardiac dulness 3.5 by 13.5 cm.

November 18, 1918. E. K. shows auricular fibrillation.

November 26, 1918. Pulse regular and remained so until discharge—November 30, 1918.

CASE 12.—*Summary:* Transient atrial fibrillation in association with myocardial failure dependent on rheumatic valve lesion.

F. C., Med. No. 41200, aged 32. *Diagnosis:* Mitral insufficiency. Syphilis.

The patient had acute rheumatic fever in 1913. For the past three years there have been progressive symptoms of heart failure.

On admission on November 7, 1918, there was moderate dyspnœa. Cardiac dulness measured 5 by 11 cm. Pulse regular in force and rhythm.

November 9, 1918. E. K. shows complete A. V. dissociation.

November 13, 1918. Atrial fibrillation.

November 18, 1918. Cardiac rhythm regular.

December 24, 1918. Short attack of auricular fibrillation.

December 25, 1918. Rhythm regular.

February 1, 1919. Discharged. Pulse regular.

CASE 13.—*Summary:* Frequent attacks of auricular fibrillation associated with fatal myocardial failure dependent on arteriosclerosis.

G. P., Med. No. 41201, aged 42. (Figs. 8, 9, 10.) *Diagnosis:* Syphilis. Chronic myocarditis.

About November, 1917, the patient was taken with dyspnœa, lasting a few minutes. Since this has had numerous attacks at varying intervals, never over a few minutes in duration. Since November, 1918, there have been increasing dyspnœa and œdema.

On admission January 27, 1919, there were marked dyspnœa and œdema. Cardiac dulness 5 by 13 cm. Peripheral vessels soft.

January 27, 1919. Pulse regular in force and rhythm. 108 per minute.

January 31, 1919. Many slight attacks of tachycardia.

February 1, 1919. Sudden death.

Autopsy: Arteriosclerosis. Luetic arteritis (pulmonary). Hypertrophied heart.

CASE 14.—*Summary:* Attack of auricular fibrillation in a patient with active endocarditis associated with extensive chronic endocarditic valve lesions. Death.

I. U., Med. No. 41232, aged 39. (Figs. 1, 2, 3.) *Diagnosis:* Aortic insufficiency.

Since October, 1916, precordial pain and dyspnœa have been practically constantly present.

On admission on January 21, 1919, the patient was very ill. There was moderate fever throughout the stay in the hospital. W. B. C. not increased. Some cough. Cardiac dulness 3 by 14 cm. Pulse 108 regular, collapsing. On February 5, 1919, auricular fibrillation appeared, but was absent on February 6. February 7, 1919. Sudden death.

Autopsy: Acute aortic endocarditis. Chronic aortic, mitral and tricuspid endocarditis. Thrombosis of middle branch of right pulmonary artery.

CASE 15.—*Summary:* Two attacks of auricular fibrillation in a patient without evident heart disease. Hypertension. Cancer of œsophagus.

T. L., Med. No. 41792, aged 68. *Diagnosis:* Carcinoma of œsophagus. Hypertension.

The patient gives history of œsophageal obstruction. Emaciated. On admission May 2, 1919, there was no evidence of cardiac disease, but the blood-pressure was 210/110. Pulse regular. On two successive Sundays the heart rate became rapid and there was a pulse deficit. Radial pulse irregular in force and rhythm.

CASE 16.—*Summary:* Short attack of paroxysmal fibrillation in a patient with hypertension and mild symptoms of myocardial weakness.

G. L. D., Med. No. 42125, aged 50. (Figs. 4 and 5.) *Diagnosis:* Hypertension. Chronic myocarditis. Obesity.

First admitted to the hospital in February, 1919, complaining of dizziness, precordial distress and some palpitation for the past three months. Pulse regular. Heart not enlarged. Blood-pressure elevated. On June 18, 1919, he felt his heart fluttering and entered the hospital. The findings were as before, except that the pulse was totally irregular and there was a pulse deficit. An E. K. taken at this time showed paroxysmal auricular fibrillation. The next day the pulse was regular and an E. K. showed a normal rhythm. January 1, 1920. Cardiac rhythm regular.

CASE 17.—*Summary:* Attack of transient auricular fibrillation in a patient, the subject of advanced renal and myocardial disease and hypertension.

I. L. D., Med. No. 42714, aged 55. *Diagnosis:* Chronic nephritis. Hypertension. Arteriosclerosis.

There have been dyspnœa and œdema of the ankles since November, 1918, gradually becoming worse. In April, 1919, the pulse was regular; heart enlarged; B. P. 155/55; phenolsulphonephthalein excretion 22 per cent in two hours; secondary anæmia; hyposthenuria.

On admission on September 22, 1919, there were marked dyspnœa and œdema. Cardiac dulness measured 5 by 14 cm. Pulse regular in force and rhythm, vessel walls thickened.

On October 3 the pulse became irregular and remained so until October 12, 1919. From that time on the cardiac rhythm was normal until discharge—November 14, 1919.

CASE 18.—*Summary:* Numerous paroxysms of auricular fibrillation during two years in an elderly woman with mild symptoms of myocardial weakness.

G. P., Med. No. 30821, aged 58. *Diagnosis:* Paroxysmal auricular fibrillation.

For two years patient has suffered from attacks of dyspnœa and palpitation, repeated at frequent intervals and lasting from a few hours to a few minutes. During two attacks the electrocardiograms showed auricular fibrillation and between the attacks perfectly normal sequence. Blood-pressure normal. The heart is not enlarged nor is there dyspnœa except on exertion. R. C. D. 3.5 by 7.5 cm.

REFERENCES

1. Cushny: On the Interpretation of Pulse Tracings. Jour. Exp. Med., 1899, IV, 327.

2. Cushny and Edmunds: Paroxysmal Irregularity of the Heart and Auricular Fibrillation. Am. Jour. Med. Sci., 1907, CXXXIII, 66.

3. Mackenzie: Diseases of the Heart. London, Second Edition. Chapter on Auricular Fibrillation.

4. Hering: Ueber die häufige Kombination von Kammervenenpuls mit Pulsus irregularis perpetuus. Deutsche med. Woch., 1906, XXXII, 213.

5. Lewis: Auricular Fibrillation. Heart, 1909-10, I, 262.

6. Rothberger und Winterberger: Ueber Vorhofflimmern und Vorhofflattern. Arch. f. d. Gesammt. Physiolog., 1914, CLX, 42.

7. Cohn: Quoted from Levine, 19.

8. Krumbhaar: Transient Auricular Fibrillation—An Electrocardiographic Study. Arch. Int. Med., 1916, XVIII, 263.

9. Heitz: La forme paroxystique de l'arythmie complète. Ann. de méd., 1914, I, 483.

10. Hornung: Ueber atypische tachycardische Paroxysmen. Deut. Arch. f. klin. Med., 1907, XCI, 469.

11. Hewlett: Clinical Observations on Absolutely Irregular Pulse. Jour. Am. Med. Assn., 1908, LI, 655.

12. Lewis: Paroxysmal Tachycardia, the Result of Ectopic Impulse Formation. Heart, 1909-10, I, 262.

13. Fox: Transitory Delirium Cordis. Amer. Jour. Med. Sci., 1910, CXL, 815.

14. Lewis and Schleiter: The Relation of Regular Tachycardia of Auricular Origin to Auricular Fibrillation. Heart, 1911-12, III, 173.

15. Robinson: Transient Auricular Fibrillation in a Healthy Man Following Hydrogen Sulfide Poisoning. Jour. Am. Med. Assn., 1916, LXVI, 1611.

16. Robinson: Transient Auricular Fibrillation. Arch. Int. Med., 1914, XIII, 298.

17. Fahrenkamp: Zur Kenntnis der vorübergehenden Arrhythmia perpetua mit Beobachtungen über Vagusdruck. Deut. Arch. f. klin. Med., 1917-18, CXXIV, 88.

18. Fahrenkamp: Vorübergehende komplette Herzunregelmässigkeiten unter dem klinischen Bilde der Arrhythmia perpetua. Deut. Arch. f. klin. Med., 1914, CXVII, 1.

19. Levine: Auricular Fibrillation. Some Clinical Considerations. Amer. Jour. Med. Sci., 1917, CLIV, 43.

20. Weiser: Zur Kenntnis der Folgen plötzlich ein- und aussetzender Arrhythmia perpetua. Deut. Arch. f. klin. Med., 1917-18, CXXIV, 303.

21. Falconer and Dean: Observations on a Case of Heart-Block Associated with Intermittent Attacks of Auricular Fibrillation. Heart, 1911-12, III, 247.

22. Schwartzmann: Ueber einen Fall von Herzblock mit paroxysmalem Vorhofflimmern. Zntribl. für inner Med., 1914, XXXV, 1001.

23. Gossage and Hicks: On Auricular Fibrillation. Quart. Jour. Med., 1913, VI, 435.

BIOGRAPHY OF SIR WILLIAM OSLER

Lady Osler has requested me to prepare a biography of her husband, and I will be most grateful to anyone who chances to see this note, for any letters or personal reminiscences, or for information concerning others who may possibly supply letters.

Copies of all letters, no matter how brief, are requested, and if dates are omitted it is hoped that they may be supplied if possible.

If the originals are forwarded for copy they will be promptly returned.

HARVEY CUSHING, M. D.,
Peter Bent Brigham Hospital,
Boston, Mass.

DR. FLORENCE RENA SABIN.

PRESENTATION TO THE UNIVERSITY OF THE PORTRAIT OF DR. FLORENCE RENA SABIN[1]

Dr. Sabin graduated from the Medical School of this University in 1900. After serving for a year as an interne in the hospital, she joined the anatomical staff under Dr. Mall, and was subsequently promoted from one grade to another until in 1917 she was made professor of histology. She is the first woman to attain the rank of a full professor in this university.

In her services as a teacher she has taken part in the instruction of over a thousand students, most of them young men. It might have been supposed that some of these young men would have objected to being put under a woman teacher, since a majority of them came from men's colleges in which such a relationship was regarded with disfavor to say the least. As a matter of fact there was never the least indication of a reaction of this kind. From the beginning Dr. Sabin succeeded in winning the confidence and regard of her students both men and women. She has been a conspicuously able and successful teacher not only in the matter of imparting sound knowledge, but also in the more difficult art of discovering the gifted student and stimulating him to independent work beyond the established routine of the classroom or the text-book. In this respect she has added example to precept, for from the beginning of her connection with the staff of the Medical School she has been a productive investigator. Early in her career she published a remarkable research upon the lymphatic system. By means of an ingenious method skillfully applied she was able to discover the mode of origin and development of the lymphatic vessels of the body. This paper was awarded the $1000 prize offered by the Naples Table Association " for the best scientific thesis written by a woman embodying new observations and new conclusions based on independent laboratory research." It has since received, I believe, a much greater reward in the universally favorable recognition accorded to it by all anatomical writers interested in this field. There followed a series of contributions bearing upon the same general subject and appearing in various scientific journals here and abroad. The results of this work have been so important as to connect Miss Sabin's name indissolubly with this topic in medical literature. Her own contributions as well as those made by other workers she has summed up and discussed in a notable lecture delivered in 1915 before the Harvey Society of New York. This is not an appropriate occasion for enumerating all the scientific publications made by Dr. Sabin, but I cannot refrain from noting that in her last paper, appearing in the Mall Memorial Volume, 1919, she has made a contribution to our knowledge of the origin and development of the blood and blood vessels which is as fortunate and significant as her work on the lymphatic system. The course of years and the increasing complexity of her duties have not diverted nor diminished her capacity for investigative work. These and other papers have established Dr. Sabin's reputation as a leading authority in her subject and have brought to her recognition and honors in the scientific world. Smith College, her Alma Mater, conferred upon her the honorary degree of Doctor of Science, and several institutions have attempted to attract her to posts in their faculties. One interesting call of this kind was to the Chair of Anatomy in the Woman's Medical College, London.

When I think of Miss Sabin's work in the Medical School it seems to me that she has been an ideal university professor. Successful in teaching, productive in research, conscientious and cooperative in all routine duties of an administrative character. Following the admonition of Pasteur she has chosen to dwell in the serene peace of the laboratory and library, and in this environment has given her time and best energies to the work belonging to her position. The professor who prefers to use his talents in the wider life outside the library and laboratory may become a useful citizen or even a public benefactor, but nevertheless he fails in his major duty to his university and his science—for none of us can successfully serve two masters.

To Dr. Sabin as a scientist we must give our admiration and respect, but those of us who have been brought into daily association with her know that to ability of a high order there is added a rare combination of good qualities which confer upon her a rich personality. Sane and fair in her judgments, modest and unassuming in her actions, loyal, helpful and unselfish, she has by contrast an emotional side easily aroused in defense of a cause or a friend and not incapable of transforming a calm scientist into a warm partisan. Some such human factor is essential to give color and timbre to the more sober professorial attributes if a sympathetic understanding is to be reached between teacher and student. I fancy that Dr. Sabin's impulsive sincerity has helped greatly to open the way to the hearts of her pupils and friends.

In offering this painting to the University, Mr. President, we, her colleagues, students and friends, feel that it will be a matter of especial interest in the history of the Medical School to have preserved a portrait of its first woman professor, one of its most distinguished graduates and one who has contributed so much of real worth to the building up of the School and to the establishment of its reputation as a center of medical research.

[1] Remarks made at the Commemoration Day Exercises, February 23, 1920, by Dr. William H. Howell.

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DETERMINATION OF THE ACIDITY OF GASTRIC CONTENTS

I. DETERMINATION AND SIGNIFICANCE OF ACIDITY

By ALFRED T. SHOHL, Baltimore

(From the James Buchanan Brady Urological Institute of The Johns Hopkins Hospital)

In acidity, the gastric juice is unique among all the body fluids. The blood is practically neutral and is maintained so with great constancy. Milk and saliva are about three times, the average urine twenty times, and sweat a hundred times, as acid as the blood. Gastric juice is a million times more acid than the blood. This acidity, as has long been known, is due to the presence of free hydrochloric acid. Clinically, the amount of acid is determined in the gastric contents after a test meal. That there are variations in the acidity of such contents is evidenced by the absence of HCl in cancer of the stomach and the high acidity in gastric ulcer. The practical importance of the determination is beyond dispute.

Nature of Solutions.—Since Prout, in 1824, showed that HCl was present in gastric contents and determined it quantitatively, and Szabo, in 1877, devised a method for titrating the HCl, our understanding of the nature of acidity has made great progress. Van't Hoff, in 1885, proved that substances dissolved in water behave like gases and follow the three gas laws: (1) Law of Boyle: The pressure increases proportionally as the volume decreases, for a given amount of gas; conversely, for a given volume of gas the pressure is proportional to the amount of gas present. (2) Law of Charles: For a given volume of gas the pressure increases as the absolute temperature. (3) Rule of Avogadro: All gases in amounts equal to their molecular weight, taken in grams, at equal temperature and pressure, occupy the same volume. In solutions one cannot, as in gases, measure the pressure directly, but it exists and is called osmotic pressure. It is a measure of the solution's capacity to draw water through a semi-permeable membrane. In terms of solutions, according to Van't Hoff, these laws become: (1) The osmotic pressure is proportional to the amount of substance present; (2) the osmotic pressure increases as the absolute temperature; (3) amounts of substances equivalent to their molecular weight, taken in grams, under similar conditions, exert the same osmotic pressure. Substances which increase osmotic pressure also raise the boiling point and lower the freezing point of solutions. The first and third laws of solutions may therefore be written: (1) The elevation of the boiling point or the depression of the freezing point is proportional to the amount of substance present; and (3) amounts of substances equivalent to their molecular weight, taken in grams, exert an equal effect on the elevation of the boiling point or on the depression of the freezing point.

Electrolytes.—Arrhenius, in 1887, showed that certain substances do not follow these laws exactly. Substances which act abnormally in solution—acids, bases and salts—he grouped into one class, and because they and no others conduct electricity, he called them "electrolytes."

Acids, bases and salts show a greater osmotic pressure and greater effect on the boiling point and freezing point than do non-electrolytes. As an explanation of their action, Arrhenius then proposed the ionic theory. Electrolytes conduct electricity because each molecule dissociates or splits into two parts, called ions, which carry electric charges. These ions are called, respectively, the *anion* and *cation*. The anion carries the negative charge and the cation the positive. When electricity is passed through the solution, the anion, or negatively charged ion, goes to the positive pole and the cation, or positive, goes to the negative pole. Thus, if each molecule dissociates into two ions, there are twice as many parts in solution, and there is twice as great an effect on the osmotic pressure, the boiling point and the freezing point.

Acids.—Acids on dissociation always give hydrogen ions as the cations regardless of the kind of acid. Hydrochloric acid dissociates into H and Cl. One represents ionized hydrogen as H^+ and ionized chlorine as Cl^-. Bases on dissociation always give hydroxyl ions as the anions, regardless of the kind of base. One represents hydroxyl ions as OH^-. A solution is acid when there are more H^+ than OH^- in solution. A solution is alkaline when the OH^- are more numerous. If both are present in equal amount, the solution is neutral. Water itself dissociates into H^+ and OH^- and partakes therefore of the nature of both acid and base. These ions are present in equal amount and so water is neutral. We may represent this in chemical notation as:

$$H_2O \rightleftharpoons H^+ + OH^-.$$

The equilibrium which has been expressed above means that water dissociates into its ions at the same speed at which the ions unite to form water. This is an example of the law of mass action: The speed of reaction is proportional to the concentration of the interacting substances. When equilibrium is established, the speed in either direction is the same. The amount of ions formed fixes the numerical value of the equilibrium, for the product of the hydrogen times the hydroxyl ions divided by the amount of undissociated water is a constant. The total number of ions present depends on the nature of water and is constant for any temperature. Representing the value of this constant by the symbol K and concentration by symbols in parenthesis, the chemical equation follows:

$$\frac{(H^+) \times (OH^-)}{(H_2O)} = K \qquad (1)$$

or

$$(H^+) \times (OH^-) = K(H_2O); \qquad (2)$$

or since the amount of water is so large in proportion to the number of ions, one may consider the amount of undissociated water as unity and write the equation

$$(H^+) \times (OH^-) = K. \quad (3)$$

This constant of water has been measured accurately. At 20° C. its value is

$$10^{-14} \text{ or } .00000000000001.$$

Since $(H^+) = (OH^-)$ the equation may be written:

$$(H^+) \times (H^+) = 10^{-14}, \quad (4)$$

or

$$(H^+)^2 = 10^{-14}, \quad (5)$$

or

$$(H^+) = 10^{-7}. \quad (6)$$

Expression of Acidity.—In measuring the acidity of solutions, one measures the amount of hydrogen ions per liter or the hydrogen-ion concentration per liter. One expresses the hydrogen-ion concentration in terms of a fraction of a gram of hydrogen ions per liter. The hydrogen-ion concentration of pure neutral water is 10^{-7}. A solution is acid when the (H^+) is greater than 10^{-7}, or alkaline when the (H^+) is less than 10^{-7}.

In one liter of normal HCl there is one gram of hydrogen, for normal solutions of monobasic acids contain the molecular weight of the substance taken in grams. Since the atomic weight of hydrogen is 1, all normal solutions of acid contain one gram of hydrogen per liter, tenth normal solutions contain .1 gram of hydrogen, etc.

TABLE 1*

	Hydrogen-ion concentration		pH	Hydroxyl-ion concentration		pOH
Acid solutions	1×10^{0}	1.0 N	0.0	1×10^{-14}	0.00000000000001 N	14.0
	1×10^{-1}	0.1 N	1.0	1×10^{-13}	0.0000000000001 N	13.0
	1×10^{-2}	0.01 N	2.0	1×10^{-12}	0.000000000001 N	12.0
	1×10^{-3}	0.001 N	3.0	1×10^{-11}	0.00000000001 N	11.0
	1×10^{-4}	0.0001 N	4.0	1×10^{-10}	0.0000000001 N	10.0
	1×10^{-5}	0.00001 N	5.0	1×10^{-9}	0.000000001 N	9.0
	1×10^{-6}	0.000001 N	6.0	1×10^{-8}	0.00000001 N	8.0
Neutrality	1×10^{-7}	0.0000001 N	7.0	1×10^{-7}	0.0000001 N	7.0
Alkaline solutions	1×10^{-8}	0.00000001 N	8.0	1×10^{-6}	0.000001 N	6.0
	1×10^{-9}	0.000000001 N	9.0	1×10^{-5}	0.00001 N	5.0
	1×10^{-10}	0.0000000001 N	10.0	1×10^{-4}	0.0001 N	4.0
	1×10^{-11}	0.00000000001 N	11.0	1×10^{-3}	0.001 N	3.0
	1×10^{-12}	0.000000000001 N	12.0	1×10^{-2}	0.01 N	2.0
	1×10^{-13}	0.0000000000001 N	13.0	1×10^{-1}	0.1 N	1.0
	1×10^{-14}	0.00000000000001 N	14.0	1×10^{0}	1.0 N	0.0

*From Henderson (1919), page 482.

To write out the actual value of such small fractions as millionth normal or millionth of a gram of ionized hydrogen is cumbersome, and to represent graphically one-tenth of a gram and one thousand millionth of a gram is impossible, unless one uses logarithmic notation. Sörensen suggested this form of expression because in the electrometric method the results are calculated from a formula in which the negative logarithm of hydrogen-ion concentration is an essential part. This he writes with the symbol pH. It is the negative exponent of ten expressed as a positive number. By pH the hydrogen-ion concentration is characterized quite as well as if it were converted into the actual number, and is used even in the case of alkaline solutions. Thus, in tenth normal acid (assuming all the hydrogen to be ionized) $(H^+) = .1$ or 10^{-1} or pH 1.0. In hundredth normal acid $(H^+) = .01$ or 10^{-2} or pH 2.0. As the hydrogen ions increase in number, the hydroxyl ions must decrease in number, since their product equals 10^{-14} (equation 3). Thus, pH 10.0 or pOH 4.0 represent the same solution. Table 1 gives the values of pH by whole numbers. All the figures in the same horizontal line represent the same solution. Thus, neutrality is shown by 1×10^{-7} hydrogen ions per liter, .0000001 N hydrogen ions, pH 7.0, 1×10^{-7} hydroxyl ions per liter, .0000001 N hydroxyl ions and pOH 7.0.

TABLE 2*

pH	Number	pH	Number
1.0	1×10^{-1}	1.7	2.0×10^{-2}
1.1	7.9×10^{-2}	1.8	1.6×10^{-2}
1.2	6.3×10^{-2}	1.9	1.2×10^{-2}
1.3	5.0×10^{-2}	2.0	1.0×10^{-2}
1.4	4.0×10^{-2}	2.1	7.9×10^{-3}
1.5	3.2×10^{-2}	2.2	6.3×10^{-3}
1.6	2.5×10^{-2}	2.3	5.0×10^{-3}

*From Clark and Lubs (1917), page 13.

The fractional values of pH may be obtained as follows: 1×10^{-2} = pH 2.0; 2×10^{-2} = pH 1.7, for the logarithm of 2.0 is .3. This, added to the exponent -2.0 = -1.7 and, the minus sign being understood, equals pH 1.7. Table 2 gives the values in numbers for every tenth pH.

It will be noted that the more acid solutions are represented by the smaller pH values. For pH 1.0 is more acid than pH 1.3. Since these numbers are exponents every even pH represents a tenfold increase in acidity. Thus pH 1.0 is ten times as acid as pH 2.0; and pH 1.0 is a hundred times as acid as pH 3.0.

Strength of Acids.—The H^+ (hydrogen ion) is the portion of any acid which gives to it its acid character. The (H^+) (hydrogen-ion concentration) determines the degree of activity of the acid. The slightly dissociated acids we call weak; those highly dissociated, strong. Acetic and carbonic acids are weak acids. HCl is a very strong acid. In the same concentration, HCl has fifty times as many ions as acetic acid or a thousand times as many ions as carbonic acid, and is proportionally active. Table 3 gives the pH of HCl and acetic acid solutions.

The very strong acids, as HCl, show a characteristic which the weaker acids do not possess—the dissociation increases

with the dilution. Tenth normal HCl is about 91 per cent dissociated; hundredth normal, 96 per cent; and thousandth normal almost 100 per cent. The important factor of the pH is the amount of acid present, for if one dilutes normal HCl tenfold, there is very little more than one-tenth the hydrogen-ion concentration.

The strength of acids may be compared by their dissociation or ionization constants. For weak acids one may show by an application of the mass law exactly as has been shown for water (equation 1)

$$\frac{(H^+) \times (A^-)}{(HA)} = K, \qquad (7)$$

or

$$(H^+) = K \frac{(HA)}{(A^-)}, \qquad (8)$$

where (H^+) is the hydrogen-ion concentration,
(A^-) is the anion concentration.
(HA) is the concentration of the undissociated acid.
K is the dissociation constant of the acid.

When the concentration of the acid which is undissociated is equal to the dissociated part, or, in other words, when the acid is half dissociated, one may write the equation:

$$\text{When } (A^-) = (HA) \text{ then } (H^+) = K,$$

and the (H^+) is the dissociation constant.

Since it is not possible always to determine the half dissociation point, it is convenient to determine the dissociation constant in another way. The salts of weak acids are almost completely dissociated, yielding a large number of the same anions as those of the acid. By the mass law, the ionization of the acid is repressed, and in amount proportional to the amount of salt present. Thus, assuming the salt to be completely dissociated and applying an equation similar to equation 7, one finds

$$(H^+) = K \frac{(HA)}{(MA)} \qquad (9)$$

where (HA) is the acid and (MA) is the salt present. When $(HA) = (MA)$, then $(H^+) = K$. In other words, when the amount of salt is equal to the amount of acid, the (H^+) is the dissociation constant of the acid.

TABLE 3 *

pH OF HCl AND ACETIC ACID

	pH
1. N HCl	.10
0.1 N	1.07
0.01 N	2.02
0.001 N	3.01
0.0001 N	4.00
1. N CH_3COOH	2.36
0.1 N	2.86
0.01 N	3.36
0.001 N	3.86

* From Michaelis (1914), page 23.

TABLE 4 *

DISSOCIATION CONSTANTS OF SOME ACIDS

		pH
Salicylic	1.0×10^{-3}	3.0
Tartaric	1.0×10^{-3}	3.0
Hippuric	2.2×10^{-4}	3.65
Acetacetic	1.5×10^{-4}	3.82
Lactic	1.35×10^{-4}	3.85
Carbon dioxide	3.0×10^{-7}	6.52
Acetic	1.86×10^{-5}	4.75
Boric'''	1.7×10^{-9}	8.79

* From Michaelis (1914), page 11.

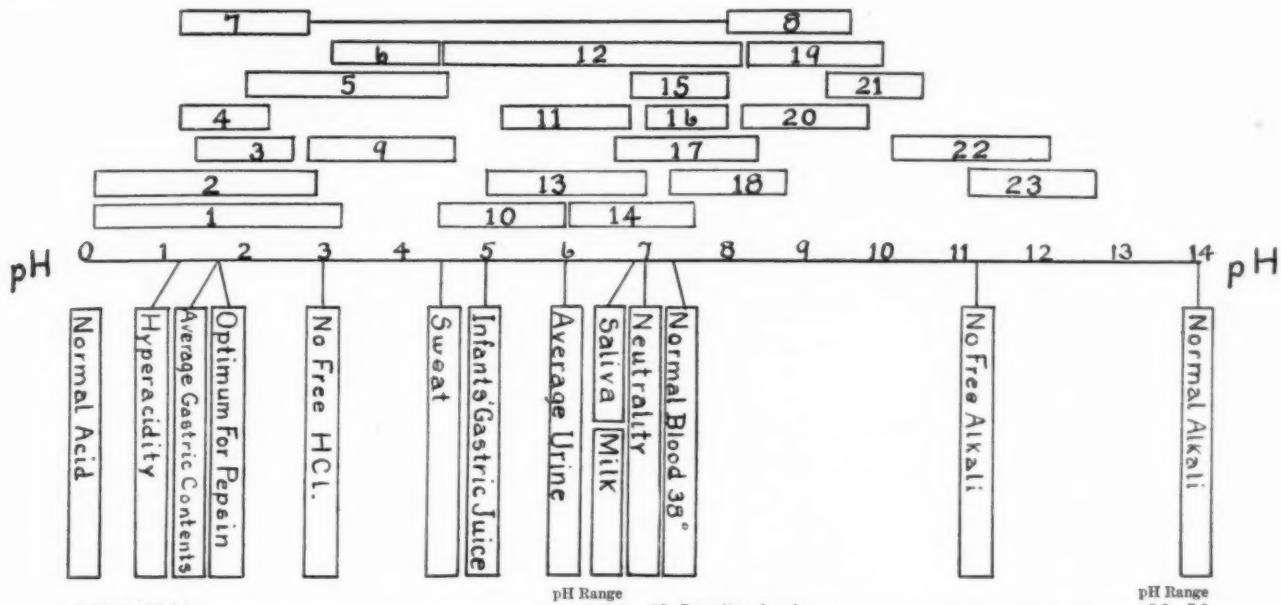
Thus, when the acid is half dissociated, or when a weak acid is present with an equal amount of its salt, the (H^+) or pH gives a direct numerical value to K or the dissociation constant. The greater the value of K, the stronger the acid. Table 4 gives the dissociation constants of some acids in terms of the numerical value and also of pH.

Determination of Acidity.—The strength of acids is subject not only to theoretical consideration, but also to experimental verification. Sörensen (1909-12), Michaelis (1914), Clark and Lubs (1916-17), have given details of the methods. The two principal methods in use are: (1) The electrometric, and (2) the colorimetric.

1. *Electrometric Method.*—The standard method is the hydrogen electrode, or gas chain, or electrometric. This is based upon the principle originated by Nernst, that if one connects two solutions of the same substance, in different concentrations, a current is produced which is proportional to the difference in concentrations. Conversely, if one knows the concentration of one solution and the voltage, one can calculate the concentration of the other. This principle has been applied to determine the hydrogen-ion concentration of any solution. One connects the sample on the one side with platinized platinum saturated with hydrogen and on the other side with a calomel-mercury-KCl cell. From the voltage given, one calculates the hydrogen-ion concentration of the solution. This method requires expensive apparatus and is so difficult that only specially equipped laboratories can use it. It is also so time-consuming that few determinations can be made in a day. Because of its accuracy, however, new problems necessitate its use.

2. *Colorimetric Method.*—Based upon measurements made by the electrometric, Sörensen devised the colorimetric method. Indicators are used to measure the hydrogen-ion concentration. There is a zone of hydrogen-ion concentration in which each indicator develops its characteristic color changes. The method requires a series of standard buffer solutions of which the pH is accurately known. One adds the proper indicator, in the same amount, to equal portions of the standards and the sample. The colors are then compared and the pH of the sample is taken as the pH of the standard to which it is closest in color. This is easy and rapid, and gives values which are accurate for all clinical procedures. The essentials of this method are: (1) A set of standard buffer solutions, and (2) proper indicators.

Buffers.—The term "buffer" is the English equivalent of the German "Puffer" which Sörensen adopted from the French "tampon." It means a solution which will hold the reaction constant, or nearly so, when acid or alkali is added to it. Two types of buffer action are clearly understood. If a weak acid is present in solution with its salt, the addition of acid or alkali does not cause a great change in reaction, for the acid is only slightly dissociated and the salt is almost completely dissociated. The ionization of the salt represses the ionization of the acid (equation 9). The pH is dependent upon the proportion of the acid to the salt. Therefore, until all the acid has been converted into the salt, the addition of a



	pH Range
1. Methyl-Violet	.1–3.2
2. Mauvein	.1–2.9
3. Tropæolin OO	1.4–2.6
4. Metanil-Yellow	1.2–2.3
5. Red Cabbage	2.0–4.5
6. Methyl-Orange	3.1–4.4
7. Thymol-sulphon-phthalein (acid range)	1.2–2.8
8. Thymol-sulphon-phthalein (alkaline range)	8.0–9.6
9. Tetrabrom phenol-sulphon-phthalein	2.8–4.6
10. Methyl-Red	4.4–6.0
11. Dibrom-cresol-sulphon-phthalein	5.2–6.8
12. Azolitium	4.5–8.2
13. Paranitro-phenol	5.0– 7.0
14. Dibrom-thymol-sulphon-phthalein	6.0– 7.6
15. Neutral Red	6.8– 8.0
16. Rosalic Acid	7.0– 8.0
17. Phenol-sulphon-phthalein	6.6– 8.4
18. o-Cresol-sulphon-phthalein	7.3– 8.8
19. Phenol-phthalein	8.3–10.0
20. o-Cresol-phthalein	8.2– 9.8
21. Thymol-phthalein	9.3–10.5
22. Alizarin Yellow R.	10.1–12.1
23. Tropæolin O	11.1–12.7

FIG. 1.—End Points of Common Indicators.

strong alkali will not make the solution very alkaline, or until all the salt has been converted to the acid, the addition of a strong acid will not make the solution very acid. For example, if there is a mixture containing equal parts of tenth normal acetic acid and sodium acetate, the reaction will be pH 4.75. Not until all the acid is neutralized by the addition of an alkali will the solution be pH 7.0, or neutral; and not until all the sodium acetate has been changed into acetic acid by the addition of an acid will the reaction equal pH 3.0, or "no free HCl."

A second type of buffer action is similar to the first, but still more stable. If, upon addition of an acid or an alkali to a solution, a compound is formed which in itself is very slightly dissociated, there will be a very small change in the hydrogen-ion concentration. When a liter of fifteenth normal acid sodium phosphate, in itself a very weak acid, which gives a pH of 4.5, is neutralized with a liter of fifteenth normal alkali, it gives alkaline phosphate with a pH of 9.0. An equal change is brought about in a liter of water by 1 c. c. of the same alkali. Protein has this property of forming compounds with either acids or bases and yielding slightly dissociated compounds. In general, dibasic or polybasic acids, with one or more H^+ neutralized, are in this category.

Other substances act as buffers through their ability to absorb or adsorb acids and alkalis. Charcoal and colloids probably fall into this class. Their action is at present not well understood. The question has often arisen as to which buffer is the best. Koppel and Spiro (1914) have shown that all buffers are equally good, but that each is strongest in a certain zone. They demonstrated that the maximum buffer value occurs at the ionization constant, or when the acid and salt are present in equal amounts. Practically, one selects that buffer solution in which the ionization constant is nearest the desired pH.

Indicators.—So many indicators are available that one must use considerable judgment in selecting those most suited to gastric analysis. Controversies were carried on in the last fifty years over the advantages of certain indicators for biological fluids, such as blood and stomach contents. The difficulties have disappeared in the light of our fuller knowledge. A great many substances show changes in color in acid and alkaline solutions. If strong acids and strong bases are titrated, almost any of the common indicators can be used. That is because their "end point" or color change is within the change of pH produced by a single drop of strong acid or alkali. When protein or other buffers are present, the indicators give very different results. Fig. 1, shows the end point, or as it will be seen, end "zones" of some of the common indicators.

Indicators which give accurate values in pure solutions may be at fault in biological fluids. Indicators give false values in these fluids because of the presence in them of protein or

salt. These errors have been studied by Sörensen and, when serious, led him to reject the indicator.

To determine the pH of gastric contents, one must first define the necessary range of pH. At pH 3.0, 100 c. c. of contents equals only 1 c. c. of tenth normal free HCl. Large amounts of organic acids or acid protein may be present without increasing the pH. Hence, pH 3.0 should be taken as the least acid point for the study of free HCl. If 70 c. c. of tenth normal free HCl are present in 100 c. c., which is the maximum acidity of stomach contents, the reaction is pH 1.2. Several indicators that cover this range have been recommended for determining the pH of biological fluids. They are shown in Table 5.

TABLE 5

INDICATORS FOR ACID SOLUTIONS

	pH
1. Methyl-violet 6B extra	0.1-3.2
2. Mauvein (Grübler)	0.1-2.9
3. p-Benzol-sulphonic-acid azo-diphenylamin. Tropæolin OO	1.4-2.6
4. m-Benzol-sulphonic-acid azo-diphenylamin. Metanil yellow	1.2-2.3
5. Red cabbage	2.0-4.5
6. p-Benzol-sulphonic-acid-azo-dimethylamin. Methyl-orange	3.1-4.4
7. Thymol-sulphon-phthalein	1.2-2.8

Of this list, methyl-violet and mauvein fade rapidly, tropæolin OO in a few days. The more acid the solutions, the more rapidly they fade. Sörensen says that methyl-violet and mauvein are unreliable in the presence of salts and all the azo dyes in the presence of proteins. He does not include tropæolin OO in the list of indicators which are unreliable in the presence of protein. Christiansen found, however, that for stomach contents it is entirely unreliable. Michaelis found that methyl-orange is also unsatisfactory for stomach contents. Walbum studied red cabbage and says that it is reliable even in the presence of genuine protein, but it does not cover the range of stomach contents. Thymol-sulphon-phthalein, studied by Clark and Lubs (1917), is the only indicator which meets the requirements for determining the pH of gastric contents.

The range of neutrality is well covered by the following indicators, shown in Table 6:

TABLE 6

INDICATORS FOR NEUTRAL SOLUTIONS

	pH
1. Litmus	4.4-8.0
2. Neutral red	7.0-8.0
3. Rosalic acid	6.8-8.0
4. Phenol-sulphon-phthalein	6.6-8.4
5. Paranitro-phenol	5.0-7.0
6. Dibrom-thymol-sulphon-phthalein	6.0-7.6

The third zone of interest is when thousandth normal alkali is present so that it, like HCl, may be considered free. When 100 c. c. of solution equal 1 c. c. of tenth normal alkali, .001 N NH_3 is pH 10.27 and .001 N NaOH is pH 11.13. This range is covered by the following indicators shown in Table 7:

TABLE 7

INDICATORS FOR ALKALINE SOLUTIONS

	pH
1. Phenol-phthalein	8.3-10
2. o-cresol-sulphon-phthalein	7.2- 8.8
3. Thymol-sulphon-phthalein	8.0- 9.6
4. o-cresol-phthalein	8.2- 9.8
5. Thymol-phthalein	9.3-10.5
6. p-Nitrobenzol-azo-salicylic-acid. Alizarin yellow R	10.1-12.1
7. p-Benzol-sulphonic-acid azo-resorcin. Tropæolin O	11.1-12.7

Sörensen says that alizarin yellow R and tropæolin O are not very reliable, but that phenol-phthalein and thymol-phthalein are excellent in the presence of protein. Clark and Lubs find o-cresol-sulphon-phthalein, thymol-sulphon-phthalein and o-cresol-phthalein reliable. There has been no special biological interest in so alkaline a range, but in determining the total buffer value of stomach contents titration to the point of free alkali becomes important. The figure shows a sufficient number of tested indicators to meet all the requirements for the determination of the acidity of gastric contents by the colorimetric method.

The Acidity of Stomach Contents.—From a consideration of the pH of solutions and the strength of acids, the nature of acidity of stomach contents becomes clear. For if we add HCl to stomach contents, the hydrogen-ion concentration will not reach pH 3.0 until all the protein has been converted into acid protein and all the organic acids have been freed from their combination with protein by HCl. For this reason, the sum of all acid factors is called total acidity, of which the acidity from neutrality to pH 3.0 is combined acidity and from pH 3.0 to pH 1.2, free HCl.

Free HCl.—At pH 3.0, 100 c. c. of stomach contents represent 1 c. c. of tenth normal HCl not combined with protein. This is true regardless of the presence of large amounts of free organic acids. For if there are 100 c. c. of tenth normal lactic acid present and half is free, the acidity is 1.35×10^{-4}, or pH 3.85, and for 100 c. c. of tenth normal acetic acid of which half is free, 1.86×10^{-5}, or pH 4.75. Even in these exaggerated examples the sample would not be as acid as "no free HCl." To give accurate titration values for free HCl, an indicator must be without protein and salt errors, and have a very sharp end point at pH 3.0. According to Christiansen, none meets these conditions. Determination of the pH of gastric contents by a colorimetric method, with thymol-sulphon-phthalein, is proposed in Paper II.

Total Acidity.—The total acidity of stomach contents is the amount of free acid plus the acid combined with protein and other buffers. It is usually determined by titration with phenol-phthalein. The end point with this indicator is approximately pH 8.4-10.0 and not neutrality. For this reason, Christiansen favored the use of litmus, which changes at approximately pH 7.0, or neutrality. Only if the protein and other substances, as eaten, are neutral, does the titration to pH 7.0 represent the amount of acid produced by the stomach. In our opinion, neither of these end points, pH 7.0 nor 8.4, is

correct. It is more rational to titrate to pH 7.4. Titration value then represents the acid of the stomach contents which must be neutralized before they reach the reaction of the blood. Palmer and Henderson chose this as the end point for the titration of urine. It does not, however, and for the same reason as above, represent the amount of acid produced by the stomach. For example, let us assume that the ingested bread had a reaction of pH 3.0; then the free HCl represents the amount of acid produced by the body. The titration is too great by the amount of the combined acid. If the bread has a reaction of pH 8.0, the values obtained are less than the HCl secreted. If information of this character is desired, methods other than titration must be resorted to, for there is really no correct predetermined end point at which the total acid can be measured. This has led us to believe that measurement of the buffer value of stomach contents yields more accurate information than titration of the total acid to pH 7.0 or 8.4. A method for determining the buffer value of stomach contents by titration, using thymol-sulphon-phthalein as an indicator, is proposed in Paper III.

Significance of pH Values in Gastric Contents.—The importance of considering the acidity of stomach contents in terms of hydrogen-ion concentration becomes evident when one analyzes the recent literature on peptic digestion. Sörensen, in his work on enzymes, showed that acidity of the medium was as important a factor as temperature in enzyme action. Only within certain narrow limits of reaction is pepsin active. The optimum reaction is approximately pH 1.65 for the action of pepsin on acid egg albumen. This is in close agreement with the figures of Michaelis and Davidsohn who record the optimum for peptic action on casein as pH 1.8. Michaelis and Mendelsohn (1914) and Northrup (1919) record the optimum on edestin as well as casein at the same acidity. They show that this is due to the hydrogen-ion concentration and not to any specific qualities of HCl, since they were able to duplicate these values with another mineral acid, HNO_3, and two very strong organic acids, tartaric and oxalic. Christiansen (1912) finds the optimum for human pepsin to be pH 1.55. If the amount of acid is greater or less than this amount, the amount of protein digestion becomes smaller. Concentrations of acid greater than pH 1.3 permanently injure and finally destroy the enzyme. If the reaction is not more acid than pH 3.0, peptic action is very poor, and at pH 4.0 is almost lacking. The fact that pepsin requires a solution of definite pH for its action is supplemented by our knowledge of the reaction of the gastric juice. Foà (1905) and Tangl, working with pure gastric juice, determined the pH by the electrometric method and found it to be pH 1.3. Fränkel, Michaelis and Davidsohn, and Christiansen, found that the normal of the contents after an Ewald meal lay between pH 1.6 and 1.5. Thus the normal hydrogen-ion concentration of the gastric juice makes an ideal medium for the optimum action of pepsin.

SUMMARY

1. To determine the acidity of gastric contents by methods based upon sound principles, one must consider acidity in terms of ionization and hydrogen-ion concentration.

2. The expression of gastric acidity in terms of pH (hydrogen-ion concentration) brings out clearly the relation between acidity and peptic digestion.

BIBLIOGRAPHY

The references to the subject are too numerous to give in detail, and the following bibliography is intended merely as a source for further references:

Bayliss, W. M.: Principles of General Physiology. London, 1918, Chap. VI and VII, p. 146-225.

Höber, R.: Physikalische Chemie der Zelle und der Gewebe. 4. Aufl., Leipz., 1914, p. 808.

Talbot, H. P., and Blanchard, A. A.: The Electrolytic Dissociation Theory and Some of Its Applications. New York, 1905.

Sörensen, S. P. L.: Enzymstudien II. Ueber die Bedeutung und die Messung der Wasserstoffionenkonzentration bei enzymatischen Prozessen. Biochem. Ztschr., Berl., 1909, XXI, 131-304.

Sörensen, S. P. L.: Ueber die Messung und Bedeutung der Wasserstoffionenkonzentration bei biologischen Prozessen. Ergebn. d. Physiol., Wiesb., 1912, XII, 393-532.

Henderson, L. J.: Concerning the Relationship Between the Strength of Acids and Their Capacity to Preserve Neutrality. Am. J. Physiol., Bost., XXI, 173-179.

Henderson, L. J.: The Theory of Neutrality Regulation in the Animal Organism. Am. J. Physiol., Bost., XXI, 427-448. *Also:* Ergebn. d. Physiol., Wiesb., 1909, VIII, 254.

Michaelis, L.: Wasserstoffionenkonzentration. Berl., 1914, p. 210.

Clark, W. M., and Lubs, H. A.: Hydrogen Electrode Potentials of Phthalate, Phosphate and Borate Buffer Mixtures. J. Biol. Chem., Balt., 1916, XXV, 479-510.

Clark, W. M., and Lubs, H. A.: The Colorimetric Determination of Hydrogen-Ion Concentration and Its Application to Bacteriology. J. Bact., Balt., 1917, II, 1-35, 109-136, 191-236.

Acid Excretion

Henderson, L. J.: A Critical Study of the Process of Acid Excretion. J. Biol. Chem., N. Y., 1911, IX, 403-424.

Buffers

Koppel, M., and Spiro, K.: Ueber die Wirkung von Moderatoren (Puffern) bei der Verscheibung des Säure-Basengleichgewichtes in biologischen Flüssigkeiten. Biochem. Ztschr., Berl., 1914, LXV, 409-439.

Acidosis

Henderson, L. J.: Acidosis and the Physico-Chemical Equilibrium of the Organism. *In:* Oxford Med., 1919, I, 471-503.

Stomach Contents

Christiansen, J.: Ueber freie und gebundene Salzsäure im Mageninhalt, I, II, III, IV. Biochem. Ztschr., Berl., 1912, XLVI, 24-93. This series of articles contains an excellent account and critical study of the methods together with numerous references.

Christiansen, J.: Einige Bemerkungen über die Mettsche Methode nebst Versuchen über Aciditätsoptimum der Pepsinwirkung. Biochem. Ztschr., Berl., 1912, XLVI, 257-287.

Fraenckel, P.: Die Wasserstoffionenconcentration des reinen Magensaftes und ihre Beziehungen zur elektrischen Leitfähigkeit und zur titrimetrischen Acidität. Ztschr. f. exper. Path. u. Therap., Berl., 1905, I, 431-438.

Foà, C.: La réaction du suc gastrique, étudiée par la methode électrométrique. Compt. rend. Soc. de Biol., Paris, 1905, LVI, 865, and LVII, 2.

Tangl, F.: Untersuchungen über die Hydrogenionkonzentration im Inhalte des nüchternen menschlischen Magens. Arch. f. d. ges. Physiol., 1905, CXV, 64-71.

Michaelis, L., and Davidsohn, H.: Ueber Bedeutung und Messung der Magensaftacidität. Ztschr. f. exper. Path. u. Therap., Berl., 1910-11, VIII, 398-413.

Michaelis, L., and Mendelsohn, A.: Die Wirkungsbedingungen des Pepsins. Biochem. Ztschr., Berl., 1914, LXV, 1-15.

Northrup, J. H.: The Effect of Various Acids on the Digestion of Protein by Pepsin. J. Gen. Physiol., Balt., 1918-19, I, 607-612.

DETERMINATION OF THE ACIDITY OF GASTRIC CONTENTS

II. THE COLORIMETRIC DETERMINATION OF FREE HYDROCHLORIC ACID

By Alfred T. Shohl and John H. King

(From the James Buchanan Brady Urological Institute and the Gastro-Intestinal Out-Patient Department of The Johns Hopkins Hospital)

To determine the free hydrochloric acid in gastric contents a test meal is given and the contents withdrawn after a definite time. The test meal most frequently used is the one introduced by Ewald, and consists of a cup of clear weak tea or a glass of water and a piece of bread, which is withdrawn after one hour. The hydrochloric acid is then determined. According to the principles underlying them we may class the methods in three groups: (1) Titration methods; (2) methods involving chemical reactions; (3) methods for measuring the hydrogen-ion concentration.

1. *Titration.*—Ten cubic centimeters of contents, filtered or unfiltered, are titrated with an alkali and a suitable indicator. The indicators most frequently used are Töpfer's (dimethylamido-azo-benzol), methyl-orange, tropæolin OO, alizarin sulphonate, and congo paper. An alkali of known strength, usually tenth normal, is added to the contents containing the indicator until the latter changes color, or, as it is called, reaches its "end point." The color change takes place at a certain definite concentration of acid. These particular indicators have been selected because they change color at the point at which free HCl is approximately neutralized. From the number of cubic centimeters of alkali used one calculates the number of cubic centimeters of tenth normal acid in 100 c. c. of stomach contents. For example, if 5 c. c. of tenth normal alkali neutralize the acid in 10 c. c. of the sample, 50 c. c. of tenth normal alkali neutralize the acid in 100 c. c.; that is, 100 c. c. of stomach contents contain 50 c. c. of tenth normal HCl.

Care must be taken to select the indicator which has the correct end point. In pure solutions of HCl almost all indicators give approximately the same result. A single drop of alkali produces the change from acidity to alkalinity. When other substances—phosphates, carbonates, proteins or salts of organic acids—are present with the HCl, as in stomach contents, different indicators give widely different results, because these substances act as buffers. In the zone between thousandth normal acid and thousandth normal alkali, the change produced by a single drop of alkali is very small when buffers are present. The indicators change at different places in this middle zone. For this reason we are accustomed to divide the titration into two parts, the part up to thousandth normal acid, and the part from thousandth normal acid to alkalinity. The first represents the *free HCl* and the other the *combined acid,* the sum of the two equaling the *total acidity.*

2. *Chemical Reactions.*—The following two methods will serve as examples of the methods involving chemical reactions.

Günzburg's Reagent: This reagent is a mixture of phloroglucin and vanillin. Though not an indicator, since it does not change color with varying concentrations of acid, it can be used to determine the free HCl in stomach contents. When a drop of this reagent is heated with a drop of contents in a porcelain dish a chemical change takes place. If no HCl is present, a yellow color develops; if HCl is present, a red color develops. Christiansen (1912) gives an excellent account of the chemistry of and procedure with this method. Ordinarily one merely uses this method to demonstrate the presence or absence of free HCl. One can use it in titrating by repeating the procedure after each addition of alkali until the test is no longer positive.

Sahli's Reagent: This is a mixture of potassium iodide and potassium iodate, which liberates iodine in the presence of acid. The liberated iodine is titrated with thiosulphate and starch.

3. *Measurement of Hydrogen-Ion Concentration.*—The true acidity of solutions is the amount of ionized hydrogen per unit volume. For determining the hydrogen-ion concentration there are two principal methods. The more accurate is the electrometric. Developed by Sörensen (1909), it has become the standard by which all other methods for measuring acidity must be judged. The colorimetric method is less accurate but simpler. This was also developed by Sörensen, who studied the hydrogen-ion concentration of test or standard solutions made from pure chemicals. In these standard solutions, suitable indicators give a definite color value or "nuance", so that one can determine the true acidity of a sample by matching it with the color standards containing the same dye in the same amount.

Many indicators which are useful in general chemistry are unfit for the colorimetric determination of gastric contents, but a sufficient number of tested indicators are available. Hawk's "Physiological Chemistry" (Chap. VIII) contains an excellent account of the principles of the colorimetric method thus applied. There are two clinical methods based

upon the colorimetric—that of Müller (1909) and that of Michaelis and Davidsohn (1910).

Müller's method involves the use of standard solutions containing known amounts of HCl and also the indicator tropæolin OO. The stomach contents and standards are put into tubes of the same diameter and the same amount of indicator is added to each. One compares the color of the contents with the standard which most nearly matches it, and the amount of HCl is estimated. Since these indicator solutions fade, Müller has devised a color chart to replace the standards.

Michaelis and Davidsohn's method is called by the authors a rough or orientation procedure. By the use of seven properly selected indicators the range of hydrogen-ion concentration of any stomach content from alkalinity to hyperacidity can be approximately determined.

DISCUSSION

These three types of method have been critically analyzed by Michaelis and Davidsohn (1910) and by Christiansen (1912). Both used the electrometric method as a check. They agree that titration methods with indicators give false results. Some of the faults of the methods are due to the fact that the indicators are not suited to the purpose for which they were used. In some the end point is not correct, as with Töpfer's indicator; in others it is not sharp, as with methyl-orange or tropæolin OO. Again, the indicator may be unsuited to solutions containing protein or salt, as congo-red or methyl-violet. Fundamentally, however, the titration method itself is faulty, for titration of an acid gives only the total amount of the acid; it cannot give the effective amount or, in other words, the hydrogen-ion concentration. Physiologically this is the important factor. In tenth normal acetic acid there are no more hydrogen-ions than in thousandth normal HCl, for the acetic acid is only slightly dissociated. Yet tenth normal acetic acid neutralizes a hundred times as much alkali as thousandth normal HCl. The hydrogen-ion concentration of the acid determines its action in the gastric contents.

Of the chemical reagents, Günzburg's gives values that are accurate. Phloroglucin and vanillin do not react to lactic, butyric or acetic acids, so that even if these are present in the gastric contents, they will not affect the results. But the method is so tedious that it is not practical for clinical purposes. Sahli's reagent has all the disadvantages of the indicators used in the titration methods. Hawk recommends it for its sharp end point, but holds that its values are not accurate because it measures acidities other than free HCl. It does not show the effective, but only the total "free" acid.

Of the methods for measuring the hydrogen-ion concentration, the *electrometric* is so difficult that only specially equipped laboratories can use it, whereas the *colorimetric* is correct and easy to apply. However, no accurate method is at present based upon the colorimetric principle, inasmuch as all the indicators which have been used yield large errors. Müller's method was an effort to apply this procedure to obtain accurate quantitative data. That he failed has been shown by Michaelis and Davidsohn, who asserted that the method was not devised with a clear understanding of the underlying principles. This is true, but checks and corrections could have been supplied. The fact that the colors fade rapidly, as Müller himself pointed out, is a more valid objection. Christiansen (1911) showed that in the presence of protein, as in stomach contents, tropæolin OO gives results that are not accurate; hence Müller's method must be rejected.

Michaelis and Davidsohn pointed out that the indicators available were not exact, and that their method is useful merely for orientation. It requires seven indicators and seven samples. The hydrogen-ion concentration is physiologically significant in the range of only two of these indicators, methyl-violet and tropæolin OO. The information obtained is not exact enough to be of help in instituting therapeutic procedures. Nevertheless, since the colorimetric method is correct in theory, we have used it as a basis for the method which we shall now present.

COLORIMETRIC DETERMINATION OF FREE HCl

The clinical method for the determination of free HCl in gastric contents is based upon the colorimetric method for measuring hydrogen-ion concentration. We shall describe: (A) Expression of acidity; (B) standards; (C) indicators; (D) color comparator; (E) materials; (F) procedure; (G) checks and results.

TABLE 1

pH	(H^+)	N	C. c. of .1 N HCl in 100 c.c. of contents	HCl .1 N c. c.	KCl .1 N c. c.	Water up to 100 c.c.
1.3	.050	.054	54	51.0	49	
1.4	.040	.044	44	41.5	50	
1.5	.032	.035	35	33.0	50	
1.6	.025	.027	27	26.3	50	
1.7	.020	.022	22	20.5	50	
1.8	.016	.017	17	16.6	50	
1.9	.012	.013	13	13.1	50	
2.0	.010	.010	10	10.6	50	
2.2	.006	.006	6	6.7	50	
2.4	.004	.004	4	4.2	50	
2.6	.0025	.0025	2.5	2.9	50	
3.0	.001	.001	1	CH_3COOH .1N 98 c.c.	NaOH .1N 2 c.c.	

The first column shows pH, and the second (H^+). Both represent the hydrogen-ion concentration. The third column, N, represents the normality of the HCl. The fourth column represents the number of cubic centimeters of .1 N HCl in 100 c. c. of stomach contents. The last columns give the composition of the standard solutions.

A. *Expression of Acidity.*—The true acidity or hydrogen-ion concentration is calculated from the gram molecular or normal solution of HCl. A liter of normal HCl contains 1 gram of ionized hydrogen (assuming dissociation to be complete). A tenth normal solution contains .1 gram, or, written in other equivalent forms, is 10^{-1} or 1×10^{-1} or pH 1.0.

The last notation was devised by Sörensen and represents the negative exponent expressed as a number with the minus sign omitted. Thus hundredth normal HCl can be expressed as .01 N or in terms of hydrogen-ion concentration, .01 or 10^{-2} or pH 2.0.

B. *Standard Solutions.*—Standard solutions are made according to the method of Clark and Lubs (1916, 1917) from pH 1.3 to 3.0. With the exception of the least acid (pH 3.0), which is tenth normal acetic acid, they are mixtures of HCl and KCl. The amounts of HCl and KCl are given in Table 1. The color which they give with the indicator is shown in Fig. 1. If the standards are not available this figure can be used in their place. As many standards can be made as desired. To avoid making the set too bulky we have used as few as possible—pH 1.4; 1.6; 1.8; 2.0; 2.4; 3.0—six in all. For the most accurate work we recommend a series of standards made up for every .1 pH. These color differences are easily distinguishable and a closer approximation can be obtained. The excellent glycocoll and citrate standards of Sörensen cover the range of gastric acidity. The HCl and KCl standards were chosen instead because it was easier to purify the substances and to make up the solutions. For very rough work, where it is desired to know simply whether there is any or much HCl, one can make the standards by diluting tenth normal HCl. In fact, after one becomes accustomed to the method and the eye is trained to the color values, rough approximation can be made without any standards.

C. *Indicator.*—The range of acidity of stomach contents for free HCl is pH 1.2 to pH 3.0—high acidity to no free HCl. From the indicators which cover this range, we chose thymol-sulphon-phthalein (Clark and Lubs). This indicator exactly covers the range, is brilliant, permanent and free from errors due to proteins and salts. Clark and Lubs mention its applicability to stomach contents. The color of the indicator is wine red at pH 1.2, orange at pH 2.0 and yellow at pH 3.0. These are shown in Fig. 1. The color will fade gradually at high temperatures and in bright sunlight. It lasts for months if the colored standards (when not in use) are kept in a closed box at room temperature. We use a .2 per cent alcoholic solution. We make the indicator concentrated so that one drop is sufficient for each cubic centimeter of standard or sample. The drop used, which, for alcoholic solutions, an ordinary medicine dropper or pipette will deliver, is equivalent to .02 c. c. After the standards have been made, this amount of the indicator solution is added for each cubic centimeter, and the same amount for each cubic centimeter of the sample. This gives the minimum dilution of the standards and sample and is the same for both.

Inasmuch as the color of thymol-sulphon-phthalein changes most markedly at points corresponding to normal or slightly diminished gastric acidity, it is most useful in the most important range. Strongly acid solutions can be brought to this range by simple dilutions. Doubling the water halves the concentration of acid. Titration by such dilution has been suggested by Hawk. Moreover, dilution has another value. If the stomach contents are colored, they tend to obscure the color resulting from the indicator, and by adding water we dilute this extraneous color. The color of the sample will then more closely approximate one of the standards. Hence the dilution makes the color comparison more accurate for two reasons: (1) It diminishes the color interference, and (2) it brings the reaction to the acidity at which the indicator gives the sharpest readings.

D. *Color Comparator.*—It is convenient to use a small color comparator such as has been described by Walpole (1911). The principle is to examine the tubes by transmitted light. The tubes are placed in a frame which cuts off the light around them and exposes them only through a small circular opening. There should be three compartments side by side, so that the sample may be placed between the two standards nearest in color. By rearranging the order of the tubes the difference in color appears more marked. Each compartment should be deep enough to hold two tubes. This facilitates the reading of colored or turbid solutions. A tube of contents without any indicator is placed behind the standard in each of the two end compartments, and in the middle compartment a tube of clear water is placed behind the contents containing the indicator. In this way very dark or turbid contents can be sharply read. A diagram, Fig. 2, shows the arrangement of the tubes.

The colorimeter is shown closed, in Fig. 3; opened, in Fig. 4; opened and the tubes properly arranged, in Fig. 5; and in position for reading, in Fig. 6. The purpose of the lid is to cut off all light except that which comes through the ground glass. The partitions are to prevent light from being reflected from the adjacent tubes. The movable sleeve protects the tubes from light when not in use. We wish to express our thanks to Dr. H. H. Young and Dr. D. M. Davis for helpful suggestions in planning the mechanical details of the colorimeter, and to Mr. H. I. Hughes for the construction of the model in the Brady Urological Institute experimental instrument shop.

If no color comparator is available, the tubes can be placed in a small test tube-rack on the window-sill. At a distance of from 6 to 10 feet, the colors appear sharper. The comparator is, however, more satisfactory.

E. *Material.*—Our material consisted of gastric contents removed one hour after an Ewald test meal of 250 c. c. of water and 25 grams of bread. A few cases of contents from fasting stomachs are included in our series. The contents were either filtered or unfiltered. In the latter case we centrifuged at high speed for 10 minutes and drew off the supernatant fluid. In this way we obtained considerably more material and thus had a supply for duplicates and checks on the method. A good many of the contents were turbid or colored and some contained a small amount of bloody mucus, but all samples were accepted for analysis.

F. *Procedure.*—Take 2 c. c. of filtered or centrifuged contents recovered from an Ewald test meal in a test-tube 11 mm. in diameter. Add two drops or .04 c. c. of .2 per cent thymol-sulphon-phthalein in 95 per cent alcohol. Place in a color

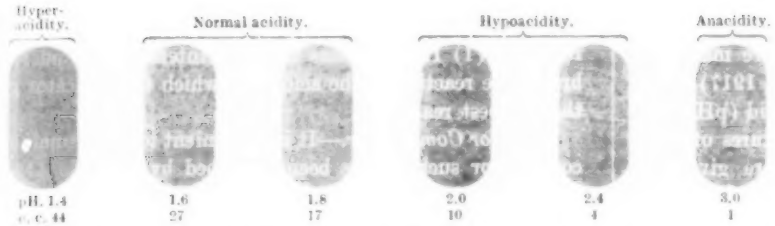


FIG. 1.—Shows the color nuance of standard solutions containing .02 c. c. of .2% thymol-sulphon-phthalein in alcohol, per c. c. of solution, and also the corresponding value in terms of pH and in c. c. of tenth normal HCl per 100 c. c. of gastric contents.

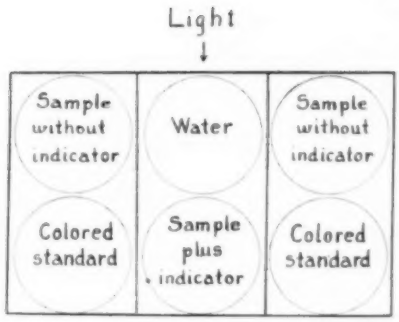


FIG. 2.—Diagram, showing the arrangement of solutions in colorimeter for making a colorimetric determination.

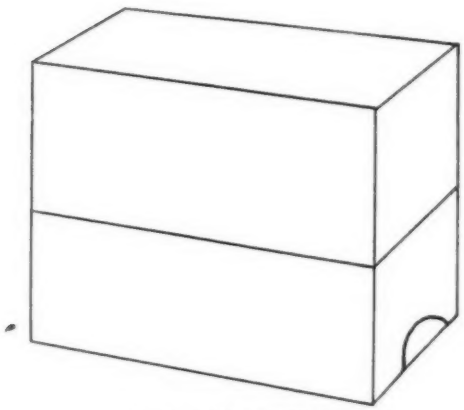


FIG. 3.—Colorimeter closed.

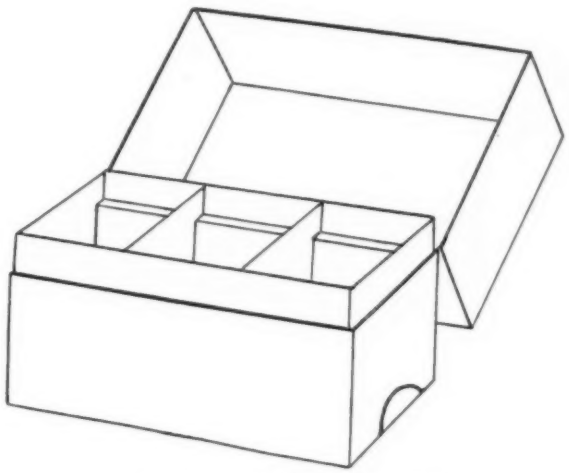


FIG. 4.—Colorimeter ready to receive tubes.

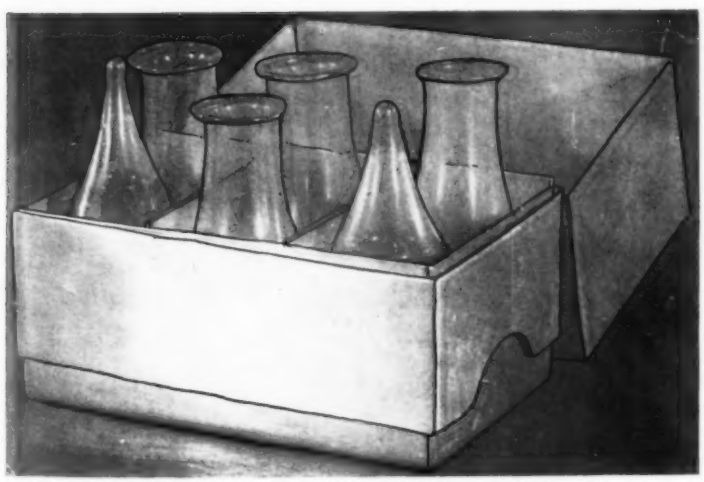


FIG. 5.—Colorimeter and tubes in position.

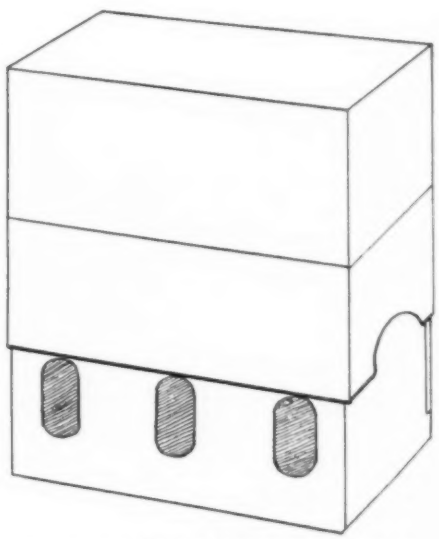


FIG. 6.—Colorimeter in position for reading.

comparator with the standards nearest to it in color. From the figures given in Table 1 estimate the amount of acid present. The results can be read directly in terms of pH, normality, or in cubic centimeters of tenth normal free HCl per 100 c. c. of stomach contents. When the sample is more acid than pH 1.6, dilute the contents with 2 c. c. of distilled water, and add two more drops of the indicator. Multiply the reading by 2, to obtain the acidity of the original sample. Thus, pH 1.3 (54 c. c. tenth normal HCl) on dilution gives pH 1.6 (27 c. c.).

It is not necessary to use the amounts given here. The only requisites are: (1) The indicator must be in the same proportion in the standards and in the sample; (2) the tubes containing the standards and sample must be of exactly the same diameter; (3) no water must be added unless the amount is known and the necessary calculation made. This method is also applicable to stomach contents removed by the fractional method, to other test meal contents, to pure gastric juice, and to other solutions ranging from pH 1.3 to pH 3.0.[1]

G. *Checks and Results.*—The values obtained by direct reading have been checked in four ways. The results are given in Table 2. The checks are: (1) by titration with .1 N alkali, using Töpfer's indicator; (2) by titration with .1 N alkali using thymol-sulphon-phthalein as an indicator; (3) by dilution, as explained above; (4) by the electrometric method.

No determination made was omitted from Table 2. It will be seen that the values agree very closely with those obtained by the electrometric method—within .1 pH. Assuming the values by the electrometric method to be correct and expressing the results in terms of .1 N HCl per 100 c. c. of contents the average difference by our method is .3 c. c.

In this series of determinations by the colorimetric method there is only one case in which there is a significant error (No. 34). This value is too high, judged by titration with either thymol-sulphon-phthalein or Töpfer's. The explanation we offer for this is that the patient had been taking iron and salicylates, which give a color reaction with the indicator. Hence, on dilution the error becomes greater. Direct reading equals 52 c. c.; dilution with an equal volume of water equals 54 c. c.; dilution with three volumes equals 64 c. c. We have found no other drug or combination of drugs which interferes with the determination. Good values are obtained by this method in contents showing high acidities (over 50 c. c.) of free HCl, as can be seen in Nos. 5, 12, 18, 29, 32, 33 and 50. This shows that this indicator is accurate in a range in which no other indicator has proved useful. It also gives as good or better values in the lower ranges. In contents where it is questionable whether free HCl is present or absent No. 45 is of interest. Töpfer's indicator showed free HCl to be present, but by the colorimetric method and electrometric method none was present. The average value of the HCl by our method is 20.0 c. c.; by titration with thymol-sulphon-phthalein, 19.4 c. c.; by titration with Töpfer's indicator, 24.2 c. c. Since it has been seen that the colorimetric method gives values which are lower than titration with Töpfer's indicator and which agree with those of titration to pH 3.0, and also those of the electrometric method, which is "the court of last appeal," it may be inferred that this method is more accurate than those in common use. In addition it is simple and rapid enough for clinical and bedside application.

TABLE 2

CUBIC CENTIMETERS OF .1 N HCL IN 100 C. C. STOMACH CONTENTS

Number of case	Colorimetric	Titration with thymol-sulphon-phthalein	Titration with Töpfer's indicator	pH colorimetric	pH electrometric
1. G23353	9	12	15	2.1	2.0
2. 23319	2.5	2.5	3.8	2.6	2.7
3. 23324	6	6.5	17.5	2.2	...
4. H. R.	—	—7	—3	—	...
5. K. C.	64	64	63	1.3+	...
6. F54756	32	31	33	1.5	...
7. 23393	20	20	22	1.7	...
8. M. C.	—	—1	3	—	...
9. H. M.	4	4	7	2.4	...
10. H. N.	1.5	1.5	5.5	2.8	...
11. 23576	—	—1	5	—	...
12. 23607	48	52	—	1.4+	...
13. C. E.	18	19	32	1.7	...
14. 23581	—	—45	—25	—	...
15. 23553	10	12	30	2.0	...
16. 23624	16	16	20	1.8	...
17. 23751	27	28	30	1.6—	...
18. 58919	50	50	50.0	1.3	...
19. T. H.	15	14	16.5	1.8	...
20. F58991	20	21	30	1.6	...
21. 23861	1	1	3	3.0	...
22. 23871	3	3	5	2.6	...
23. 23880	5	6	11	2.3	...
24. 74040	24	23	34	1.6—	...
25. 29991	18	17	26.5	1.8+	...
26. S24089	16	17	29	1.8	...
27. G24094	13	14	26	1.9	...
28. 24276	24	26	32	1.6	...
29. 24091	53	50	55	1.3	...
30. 21452	1	1	6	3.0	...
31. F41452	15	14	21	1.8—	...
32. 9729	50	45	50	1.4+	...
33. G24279	50	51	62	1.3	...
34. 88487	52	34	39	1.3	...
35. 12442	40	40	46	1.4	...
36. F95016	—	—10	0	—	...
37. G 7582	2	2.5	8	2.6	...
38. G24429	—	—16	0	—	...
39. G24376	4	4	7.5	2.4	...
40. G17077	15	5	12	2.3	...
41. G 2379	10	11	14	2.0	...
42. C. F.	6	5.5	10	2.2	2.1
43. 26480	5	6	9	2.3	2.3
44. 37078	12	10	20	1.9	1.9
45. 27033	—	—1	10	—	3.4
46. 27354	5	5	11	2.3	2.3
47. 27418	12	10	14	1.9	1.8
48. 5986	10	12.5	14	2.0	1.95
49. 27465	2.5	3	5	2.6	2,6
50. V. F.	70	63	70	1.3+	1.2

Much stress has been laid upon the pH or hydrogen-ion concentration of gastric contents because of its importance to the clinician in interpreting stomach findings. In the previous paper, we have shown the correlation between the pH of the contents and the effect on gastric digestion. The limits of peptic digestion are pH 1.3 and 4.0 and the optimum is at pH 1.65. It seems obvious that one should correlate these important facts with medical practice. With the information

[1] All the materials necessary for carrying out the test can be obtained from Hynson, Wescott & Dunning, Baltimore. Complete sets and color comparators, as well as separate standards, tubes and indicator solution are available.

at hand we can say exactly what the optimum of the gastric contents should be and we can estimate how much acid is necessary to produce the optimum reaction in the sample which has been removed. Thus we have at the same time, in the measurement of the hydrogen-ion concentration, a method for diagnosis, an evaluation of the degree of progress and the indications for therapeutic procedures.

SUMMARY

1. A new colorimetric method is presented, which determines the amount of free HCl in the gastric contents. A simple color comparison shows both the amount and concentration of the acid.

2. The procedure is: Take 2 c. c. of filtered or unfiltered gastric contents. Add 2 drops of .2 per cent thymol-sulphonphthalein. Compare the color of the sample with standard solutions containing the same amount of the same indicator.

3. The result can be read directly in terms of pH, normality, or cubic centimeters of free tenth normal HCl in 100 c. c. of gastric contents.

4. The method is accurate and applicable to clinical tests.

BIBLIOGRAPHY

Christiansen, J.: Untersuchungen über freie und gebundene Salzsäure im Mageninhalt. 1. Bestimmung freier Salzsäure im Mageninhalt. Biochem. Ztschr., Berl., 1912, XLVI, 24-49.

Hawk, P. B.: Practical Physiological Chemistry. 5th Ed., Chap. 8, Gastric Analysis. Blakiston's Sons, Phila., 1916, 148-175.

Sörensen, S. P. L.: Enzymstudien II. Ueber die Messung und die Bedeutung der Wasserstoffionenkonzentration bei enzymatischen Prozessen. Biochem. Ztschr., Berl., 1909, XXI, 131-304.

Müller, A.: Zur Methodik, der Aziditätsbestimmung im Magensafte. Med. Klin., Berl. & Wien, 1909, v, 1430-1440.

Michaelis, L., und Davidsohn, H.: Ueber Bedeutung und Messung der Magensaftacidität. Ztschr. f. exper. Path. u. Therap., Berl., 1911, VIII, 398-413.

Christiansen, J.: Die Sauerstoffionen-konzentration im Mageninhalt. Deutsches Arch. f. klin. Med., Leipz., 1911, CII, 103-116.

Clark, W. M., and Lubs, H. A.: Hydrogen Electrode Potentials of Phthalate, Phosphate, and Borate Buffer Mixtures. J. Biol. Chem., Balt., 1916, XXV, 479-510.

Clark, W. M., and Lubs, H. A.: The Colorimetric Determination of Hydrogen-Ion Concentration and Its Application to Bacteriology. J. Bact., Balt., 1917, II, 1-35, 109-136, 191-237.

Walpole, G. S.: Chart Presentation on Recent Work on Indicators. Bio-Chem. J., Liverp., 1911, V, 207-214.

DETERMINATION OF THE ACIDITY OF GASTRIC CONTENTS

III. COMBINED ACIDITY AND BUFFER VALUE

By Alfred T. Shohl and John H. King

(From the James Buchanan Brady Urological Institute and the Gastro-Intestinal Out-Patient Department of The Johns Hopkins Hospital)

The acidity of stomach contents removed after a test meal is usually measured in several fractions. The total acidity or sum of all the acid factors is composed of free HCl and the combined acid. The combined acid is that portion which remains after the free HCl has been neutralized, and consists of (1) the combined HCl; (2) organic acids; and (3) acid salts. Experience has shown that the combined HCl is practically the same as the combined acid, for organic acids and acid salts play a very small part in gastric acidity. In cases in which no free HCl occurs, the combined acid and the total acidity are identical. Such contents are said to show an "acid deficit" represented by the amount of HCl which must be added to the sample until free HCl is just present. This value indicates the amount of acid which the stomach should secrete, or which, if it fails to secrete, must be added before gastric digestion can progress. The sum of the total acidity and the acid deficit in such cases measures the power of the contents to combine with acid. This value is comparable to the combined acid in cases showing free HCl.

There are three types of methods for the determination of combined acid. According to the principles underlying them, these are: (1) Titration methods; (2) methods involving chemical reactions; and (3) hydrogen-ion concentration measurements.

1. *Titration Methods.*—The usual procedure is to titrate 100 c. c. of contents with an alkali and a suitable indicator. The indicators most frequently used are phenol-phthalein, litmus, rosalic acid, neutral red and alizarin. These indicators have been selected because their end point is approximately that of neutrality. From the number of cubic centimeters of an alkali of known strength which are required to reach the end point of the indicator, one calculates the number of cubic centimeters of tenth normal acid in 100 c. c. of stomach contents. Titration gives the total acidity from which one must subtract the value of the free HCl. Thus, if 10 c. c. of stomach contents require 7.5 c. c. of .1 N alkali to reach the end point of phenol-phthalein, 75 c. c. of .1 N acid represent the total acid in 100 c. c. of stomach contents. If the free HCl was found to be 50 c. c., then 75 c. c. minus 50 c c. equals 25 c. c., the value of the combined acid. In practice, one usually adds two indicators to the same sample, as Töpfer's indicator and phenol-phthalein. The colors do not interfere, so that one can titrate the free HCl, and from that point determine the combined acid directly.

If no free HCl is present, one determines the total acidity by titrating with an alkali and phenol-phthalein, as above. One also titrates with an acid and Töpfer's indicator to obtain the acid deficit. These two values are added. Thus, if the total acid equal 12 c. c. of .1 N acid and the acid deficit equals 15 c. c. of .1 N acid, the sum of the two equals 27 c. c. of .1 N HCl per 100 c. c. of stomach contents. This represents the combining power of the contents.

A series of titration methods using several indicators, so as to determine separately combined HCl and organic acids, was devised at the time when it was thought organic acids were present in the stomach contents in considerable amounts and were an important factor in gastric acidity. These methods are no longer used.

2. *Methods Involving Chemical Reactions.*—As early as 1824, Prout demonstrated the presence of HCl in the gastric juice and devised a method for its measurement by determining the Cl. He differentiated that portion which was fixed to bases from that which was free in the acid. Reisner (1903) returned to this original principle. In the meantime, Hayem and Winter, and Martius and Lüttke, determined the total chlorides, making no correction for the neutral salts.

Bidder and Schmidt (1852) determined the K, Na, Ca, NH_4 and Cl, and subtracted the value of the neutral salts.

Sjörquist (1889) fused the stomach contents with $BaCO_3$, which converts the Cl attached to acid into $BaCl_2$. This is extracted with hot water, acidified and precipitated as $BaSO_4$ by sulphuric acid. From the weight of the $BaSO_4$ the amount of HCl is calculated. More than half a dozen modifications of this method have been proposed, in all of which the principle of fusion with $BaCO_3$ is employed.

All of the chemical methods determine the total HCl value, from which the free HCl must be subtracted to give the combined acidity.

3. *Hydrogen-Ion Concentration Methods.*—By measuring the hydrogen-ion concentration, one measures the true acidity. The two methods are: (1) The electrometric, and (2) the colorimetric. Both have been used by Michaelis and Davidsohn (1910) for those contents in which free HCl was present, and also for those in which there was no free HCl.

DISCUSSION

Contents which show free HCl require different consideration from those which do not, and will be discussed separately.

1. *Free HCl Present.*—(a) In titration of contents which show free HCl the combined acid can be estimated only after the free HCl has been neutralized. If there is an error in the determination of the free HCl, an error will exist also in the determination of the combined acid. Töpfer's indicator gives too high results for free HCl and hence must necessarily give too low values for combined acid. True neutrality, pH 7.0, has been the end point sought in titration methods. From what it now known of the nature of solutions and the end points of indicators, it is evident that phenol-phthalein is not an ideal indicator. Its end point is about pH 8.3-10.0, or 25-1000 times as alkaline as true neutrality. Christiansen (1912) has reviewed the methods for determining the combined acidity of stomach contents. He comes to the conclusion that phenol-phthalein gives results that are too high, and that correct results are obtained by litmus.

(b) The chemical methods are of great interest in determining the total HCl value. They were not considered important, because of the presence of other acids in the stomach contents. However, Boas (1894) showed that organic acids seldom occur. Tobora (1905) showed that acid salts, such as phosphates, are negligible. NH_3 which is combined with HCl is not sufficient to be important. Martius (1892) showed that titration with phenol-phthalein gives results comparable to Lüttke's for the combined HCl. Lüttke's method does not, however, differentiate the Cl of HCl from that of neutral salts. When this is done, as in Prout's or in Bidder and Schmidt's method, the values obtained by the determination of the HCl are comparable to values obtained by titration with litmus. Christiansen found that titrations with litmus agree very well with Sjörquist's values when corrections for the NH_4Cl are made. The combined HCl and the combined acid are therefore practically equivalent.

(c) Measurement of the hydrogen-ion concentration, in stomach contents showing free HCl, gives only the value of the free HCl. It supplies no information as to the combined acid.

2. *No Free HCl Present.*—(a) In cases which show no free HCl, titration gives a value comparable to the combined acid only when one takes the sum of the acid deficit and the total acid. If one uses the same indicators as for contents showing free HCl, the same errors will obtain. For one must titrate to two end points; for example, that of Töpfer's indicator for the acid deficit and that of phenol-phthalein for the total acidity.

(b) Methods involving chemical reactions give only the value of the HCl present. They give no information as to the acid deficit and hence can give no value for the potential combined acid.

(c) Methods for measuring the hydrogen-ion concentration give values that range from pH 3.0 to alkalinity, about pH 8.0. The electrometric method gives the reaction accurately. For approximate values, the colorimetric method of Michaelis and Davidsohn leaves little to be desired. In adult gastric contents with no free HCl, the pH is not an important factor, for no significant peptic digestion takes place until free acid is present. Measurement of the true acidity gives no information concerning the amount of acid necessary to bring the contents to neutrality or the amount of acid which must be added before digestion can progress.

BUFFER VALUE

1. *Definition.*—Buffer solutions are those to which acid or alkali can be added without causing a marked change in the reaction. They possess this property because they are either weak acids which on the addition of an alkali do not become alkaline until all the acid has been neutralized, or they are salts of weak acids which on the addition of acids do not become acid until the weak acid has been freed from its salt. In stomach contents the protein present acts as a buffer. It can combine with either acid or base, and give nearly neutral compounds. The amount of acid or alkali which can be added before the reaction reaches a definite acidity or alkalinity is called the buffer value. The amount of acid or alkali necessary to change the reaction from one hydrogen-ion concentration to another is the buffer value between those acidities. The total buffer

value is the amount necessary to change the reaction from pH 3.0, no free HCl, to pH 11.0, free alkali.

Fr. Volhard (1903) was the first to show that, in stomach contents, titrations with phenol-phthalein give higher values than those with litmus, because it is an indicator for alkaline solutions, and more alkali must be added to reach the end point. He also showed that this is due to the buffer action of the protein in the contents. What one really determines by titration methods is the buffer value to the end points of the indicators.

2. *Factors Affecting the Buffer Value.*—(a) *Concentration.*—Concerning the buffer values after different test meals, interesting problems arise. In general, one may say that the buffer value is not related to the hydrogen-ion concentration, but the hydrogen-ion concentration to the buffer value. The more concentrated the buffer solution, the greater is the amount of acid necessary to change the solution to a desired pH. For example, if there are two solutions of 100 c. c. of alkaline phosphate, the first normal and the second decinormal, and 10 c. c. of normal HCl are added to each, the first will be alkaline, pH 8.0, and the second acid, pH 4.5. This is a difference in the hydrogen-ion concentration of more than a thousandfold. Therefore, a given amount of HCl secreted by the stomach yields with different foods widely different reactions.

(b) *Hydrolysis of Protein.*—What happens to the buffer value during peptic digestion is clearly indicated by the researches of Christiansen (1912). As digestion progresses the proteins become hydrolyzed or split into polypeptids or peptones, thereby producing more free alkaline groups. These combine with more HCl, thus reducing the hydrogen-ion concentration and free HCl, and increasing the buffer value.

(c) *Other Factors.*—Extraneous buffers, among which may be carbonates regurgitated from the duodenum, blood, foreign protein or phosphates, also increase the buffer value of the contents. If less water is present, the contents are more concentrated, and the apparent buffer value of the contents is increased.

3. *Significance of Buffer Value.*—To determine accurately the amount of alkali necessary to bring a sample of contents to true neutrality has no physiological significance. Such a determination merely shows the buffer value to pH 7.0; it does not show the acid secreted by the glands of the stomach nor the amount of alkali which the body must furnish to bring the contents to the reaction of the blood.

In order to measure the amount of HCl which the stomach secretes, one must first know whether any portion of the acid has been neutralized by the alkaline duodenal contents; moreover, one must know the true acidity of the food. Bread has an average reaction of pH 5.0, but may vary greatly (Henderson and others, 1919). For example, if the bread is pH 5.0 and the stomach contents also are pH 5.0, no acid has been secreted, and we have a case of true anacidity. Yet the titration as commonly carried out will show a considerable amount of combined acid. If the bread is pH 8.0 and the stomach contents are pH 5.0, the titration represents only a portion of the acid which the stomach has secreted.

One may determine the amount of alkali necessary to bring the contents to the reaction of the blood, pH 7.4. Henderson and Palmer (1914) used this principle in determining the acidity of urine to show the amount of acid which the body had excreted in forming the urine. In the case of stomach contents, since one must examine only a sample of the total amount, the determination is quantitatively less accurate.

METHOD

The following method was devised to determine the buffer value of the contents. We shall describe: (1) Principle; (2) material; (3) indicator; (4) procedure; (5) results.

1. *Principle.*—To find the buffer value of a sample of stomach contents, one must determine the amount of acid or alkali necessary to change its reaction from pH 3.0 (no free HCl) to pH 9.6 (near the point of free alkali).

2. *Material.*—The material was the filtered or centrifuged contents recovered after an Ewald test meal of 25 grams of bread and 250 c. c. of water. The same material was used for the determination of free HCl.

3. *Indicator.*—Thymol-sulphon-phthalein .2 per cent in 95 per cent alcohol was used (Clark and Lubs (1917)). This is the same indicator that was used for the determination of free HCl. It determines both the free HCl and the buffer value of gastric contents, for it has an acid color zone red, pH 1.2-3.0; a neutral color zone yellow, pH 3.0-8.0; and an alkaline color zone green to blue, pH 8.0-9.6. The end point of phenol-phthalein is pH 8.3-10.0, and of thousandth normal alkali pH 11.1. Therefore, thymol-sulphon-phthalein gives nearly the total buffer value from free HCl to free alkali, and gives results similar to those with phenol-phthalein.

4. *Procedure.*—A. *When Free HCl is Present.*—(1) Add one drop, or .02 c. c., of .2 per cent thymol-sulphon-phthalein in alcoholic solution for each cubic centimeter of stomach contents. Titrate with .1 N NaOH free from carbonate to the full blue color of the indicator. Subtract the value of the free HCl found by the colorimetric method from the titration value.

Example.—

2 c. c. of contents neutralize 1.04 c. c. .1 N NaOH. Therefore, 100 c. c. neutralize 52 c. c. .1 N NaOH. Free HCl by the colorimetric method is 24 c. c. .1 N per 100 c. c. Therefore, 52 c. c. minus 24 c. c. equals 28 c. c. .1 N HCl, the buffer value per 100 c. c. of stomach contents.

(2) Instead of the colorimetric method for free HCl, direct titration to pH 3.0 may be made, thymol-sulphon-phthalein being used as the indicator. From this point the buffer value may be titrated directly.

B. *When no Free HCl is Present.*—(a) Add one drop of .2 per cent thymol-sulphon-phthalein for each cubic centimeter of stomach contents. Either of two procedures may then be followed to determine the acid deficit: (1) Titrate with .05 N HCl until HCl is just present, pH 3.0.

Example.—

.48 c. c. .05 N HCl required for 2 c. c. of contents.
.24 c. c. .05 N HCl required for 1 c. c. of contents.
.12 c. c. .1 N HCl required for 1 c. c. of contents.
12. c. c. .1 N HCl required for 100 c. c. of contents. Acid deficit.

(2) Add 1 c. c. of .05 N HCl and one drop of .2 per cent thymol-sulphon-phthalein. Read the value of the free HCl by the colorimetric method. Multiply this value by the number of cubic centimeters present (stomach contents plus acid), and subtract the product from 50 c. c. which is the value of the HCl added.

Examples.—

(1) 1 c. c. of .05 N HCl added to 2 c. c. of contents:

Free HCl colorimetric =	13 c. c. .1 N HCl.	50 c. c. Amount added.
Number of c. c. of sol.	3	39 c. c. Amount free.
Total amount free	39 c. c.	11 c. c. Acid deficit.

(2) 1 c. c. of .05 N HCl added to 1 c. c. of contents:

Free HCl colorimetric =	20 c. c. .1 N HCl.	50 c. c. Amount added.
Number of c. c. of sol.	2	40 c. c. Amount free.
Total amount free	40 c. c.	10 c. c. Acid deficit.

(3) 1 c. c. of .05 N HCl added to 4 c. c. of contents:

Free HCl colorimetric =	8 c. c. .1 N HCl.	50 c. c. Amount added.
Number of c. c. of sol.	5	40 c. c. Amount free.
Total amount free	40 c. c.	10 c. c. Acid deficit.

(b) To the acid deficit obtained in either of the ways given above, add the alkaline titration value. To obtain this, titrate (it is best to use another sample) with .2 per cent thymol-sulphon-phthalein as the indicator. Add .1 N NaOH free from carbonate until the full blue color is present. The sum of these two values gives the buffer value.

Examples.—

Acid deficit .....10 c. c. .1 N solution per 100 c. c. of contents
Alkali titratition ....14 c. c. .1 N solution per 100 c. c. of contents

Buffer value .....24 c. c. .1 N solution per 100 c. c. of contents

C. *Discussion.*—Thus with the first procedure for the acid deficit, the titration is more difficult and the calculation simple. With the second, the procedure is simple and the calculation longer. It is not necessary to use .05 N HCl for the titration. Provided the proper calculation is made, amounts of HCl other than 1 c. c. can be substituted. The second procedure is given so that the acid deficit may be determined when one does not desire to determine the buffer value or when no microburettes are available. A similar method may be devised to determine without microburettes the power of the contents to combine with base. Other amounts of contents can be used. Equally good results are obtained with 10 c. c. samples and an ordinary burette.

Alkali free from carbonate is essential, for if carbonate is present it acts as a buffer and higher results are obtained. Carbonate-free alkali can be prepared by making a saturated solution of NaOH, allowing the carbonate to settle out, decanting the clear solution and diluting to the desired strength with freshly boiled hot distilled water. Solutions after being made must be protected from the air by soda-lime tubes.

5. *Results.*—The results in cases showing free HCl are shown in Table 1. Column 1 gives the buffer value with thymol-sulphon-phthalein. Column 2 gives the combined acid with Töpfer's indicator and phenol-phthalein. The values were obtained by subtracting the values of the free HCl from the total alkali titration. The results in cases showing no free HCl are shown in Table 2. Column 1 gives the acid deficit with thymol-sulphon-phthalein. Column 2 gives the alkali titration with thymol-sulphon-phthalein. Column 3 gives the sum of these two values, the buffer value; the last

TABLE 1

CASES SHOWING FREE HCL

	Buffer value	Combined acid		Buffer value	Combined acid		Buffer value	Combined acid
1.	22	20	15.	49	39	29.	48	50
2.	31.5	26	16.	39	27.5	30.	43	30
3.	34	26	17.	24	14.5	31.	31	22
4.	26	18	18.	24	15	32.	31.5	27
5.	17	12.5	19.	26	20.5	33.	22	18
6.	25.5	19	20.	32	27	34.	15	13
7.	25	32	21.	11	10	35.	48.5	39.5
8.	16	11	22.	35	35	36.	15	13.7
9.	30	18	23.	24	17	37.	36	31
10.	17	20	24.	13	12.5	38.	23	21.5
11.	24.5	21	25.	19	22	39.	53	44
12.	31	25.5	26.	25	21	40.	25	20
13.	24	18	27.	26	25	41.	25	13.5
14.	30	23	28.	46	40			

Values are given in cubic centimeters of .1 N solution per 100 c. c. of stomach contents.

TABLE 2

CASES SHOWING NO FREE HCL

	Acid deficit	Alkali value	Buffer value	Total acidity
1.	16	15	31	15
2.	10	12	22	11.5
3.	15	15.5	31.5	17
4.	6	22	28	20
5.	21	10	31	10
6.	1	30	31	22
7.	1	60	61	60
8.	6	18.5	24.5	24.5
9.	9	22	31	22

Values are given in terms of cubic centimeters of .1 N solution per 100 c. c. of stomach contents.

column gives the value of the total acidity with phenol-phthalein. The buffer value in cases showing free HCl varies between 11 c. c. and 53 c. c. and in cases showing no free HCl varies between 22 c. c. and 61 c. c.

The values for the combined acid average 23.4 c. c.; the buffer value with thymol-sulphon-phthalein averages 28.3 c. c. The value for the total acidity averages 47.6 c. c.; the value for free HCl plus buffer averages 48.3 c. c. Thus the difference between the combined acidity and the buffer value is due largely to the value for free HCl with Töpfer's indicator, which is known to give too high values. If one subtracts the value of free HCl obtained by the colorimetric method from that of the total acidity obtained with phenol-phthalein, and compares the remainder with the buffer value, expressing all the values in terms of .1 N acid per 100 c. c. of stomach contents, one obtains the following: Total acidity, 47.6 c. c., minus free HCl, 20.0 c. c., equals combined acid, 27.6 c. c. The buffer value is 28.3 c. c. The buffer value in cases showing no free HCl averages 32.3 c. c.

Discussion.—The buffer value and the combined acid value, though almost equal in numerical terms, differ greatly in significance. The combined acid value signifies the amount of HCl united to the protein. The buffer value represents the amount of acid or base required to bring about a definite change in reaction. The buffer value by our method is lower than that which would be obtained by titrating with another indicator to pH 11.0; but the important factor is to determine the buffer value between any two known points. The method proposed determines neither the acid production nor the acid value of the stomach contents, nor the amount of alkali necessary to bring the contents to the alkalinity of the blood. By measuring also the acidity of the food, however, these three factors can be determined from the buffer value to certain end points—to the reaction of the food for the acid secretion, to pH 7.0 for the acid value of the contents and to pH 7.4 for the amount of alkali necessary to bring the contents to the reaction of the blood. The clinical conditions, in which the buffer value of the contents is a factor cannot be discussed here; but they are important and the buffer value throws some light on their solutions. The method here presented determines the buffer value.

SUMMARY

1. A method is proposed to determine the buffer value of stomach contents by titration, using thymol-sulphon-phthalein as an indicator.

2. This indicator changes from red to yellow at pH 3.0, "no free HCl," and from green to blue at pH 8.0-9.6, near the point of free alkali. This range of the indicator gives practically the total buffer value of the protein.

3. The procedure in cases showing free HCl is: Add 1 drop or .02 c. c. of .2 per cent thymol-sulphon-phthalein in alcoholic solution for each cubic centimeter of stomach contents. Titrate with .1 N NaOH free from carbonate, to the full blue color of the indicator. Subtract the value of the free HCl obtained by the colorimetric method from the titration value.

4. The procedure in cases showing no free HCl is: Add 1 drop or .02 c. c. of .2 per cent thymol-sulphon-phthalein in alcohol for each cubic centimeter of stomach contents. First titrate the acid deficit by adding .05 N HCl until the orange color appears; or, add 1 c. c. of .05 N HCl and determine the excess by the colorimetric method. In a second sample titrate with .1 N NaOH free from carbonates and thymol-sulphon-phthalein to pH 0.6, the full blue color of the indicator. The sum of the acid deficit and the alkali value equals the buffer value.

5. In cases showing free HCl, the buffer value is nearly equal to the value of the combined acid, or in cases showing no free HCl to the sum of the acid deficit and the total acidity.

6. Determination of the buffer value can be used to determine the amount of HCl secreted by the stomach, the acid value of the contents and the amount of alkali which the body must furnish to neutralize the stomach contents.

BIBLIOGRAPHY

Christiansen, J.: Untersuchungen über freie und gebundene Salzsäure im Mageninhalt. II. Titrimetrische Untersuchungen über die Pepsinverdauung. IV. Die Bestimmung der Gesammtsalzsäure im Mageninhalt. Biochem. Ztschr., Berl., 1912, XLVI, 50-70, 82-93. These articles give a review of the literature of the subject.

Henderson, L. J., and Palmer, W. W.: On Several Factors of Acid Excretion. J. Biol. Chem., Balt., 1914, XVII, 305-315.

Clark, W. M., and Lubs, H. A.: The Colorimetric Determination of Hydrogen-Ion Concentration and Its Application to Bacteriology. J. Bact., Balt., 1917, II, 1-35, 109-136, 191-236.

Henderson, L. J., Fenn, W. O., and Cohn, E. J.: Influence of Electrolytes upon the Viscosity of Dough. J. Gen. Physiol., Balt., 1918-19, I, 387-397.

Henderson, L. J., Cohn, E. J., Cathcart, P. H., Wachman, J. D., and Fenn, W. O.: A Study of the Action of Acid and Alkali on Gluten. J. Gen. Physiol., Balt., 1918-19, I, 459-472.

MINUTE ON THE DEATH OF SIR WILLIAM OSLER

On motion of the Executive Committee of the Federation of American Societies for Experimental Biology in Cincinnati December 30, 1919, the following minute was drafted by Dr. C. H. Bunting of the committee:

In the death of Dr. Osler, the medical profession has suffered an immeasurable loss. Belonging to no cult, or age, or clime, but descended in direct line from Hippocrates, he was Master of the Art of Medicine in its purest form. As a teacher, he was again Master, painting with broad strokes pictures of disease never to be forgotten by the student. An investigator and an inspirer of investigation, a worthy counsellor of brother physicians, a delver into the history of medicine, and an ornament to its letters; and withal so human and of such rare personal charm as to be beloved of all who came in contact with him. Such was the man we mourn.

We grieve not only for the loss of leader and friend, but also that death overtook him in the very shadow of the great conflict which had brought him so great personal loss and sorrow and robbed him of the mellow years which were so fully his due.

C. H. Bunting,
Henry A. Christian,
A. S. Loevenhart,
Committee.

CONTRIBUTIONS TO PSYCHOPHARMACOLOGY*

By DAVID I. MACHT

(From the Pharmacological Laboratory of the Johns Hopkins University)

INTRODUCTORY

The effect of drugs on psychological functions has been the subject of remarkably little investigation on the part of either psychologists or pharmacologists. Of course every medical man is familiar with some such phenomena; and every student is told of the delirifacient effects of belladonna, of the xanthopsia following the administration of santonin, and of the deafness and ringing in the ears produced by quinin and salicylates. When we, however, examine the literature, it is surprising to find how few experimental contributions on the subject have been made. Only two drugs have received any adequate consideration in this respect; they are alcohol and caffein. The elaborate and exhaustive studies on alcohol by Benedict and Dodge [1] and others, and on caffein by Dietl and Vintschgau [2], and more recently by Hollingsworth [3], are most valuable contributions dealing with the effects of these drugs. Other drugs which have received some consideration in this connection in recent years are the bromides, as exemplified by the work of Loewald [4]; strychnin, as studied by Poffenberger [5] and Lashley [6]; and in some experiments performed by Münsterberg [7]. The number of contributions to the domain of what we may be permitted to call "psychopharmacology" is certainly very meagre, as compared with experimental investigations on the action of drugs along other lines. During the past five years or so the author, with the assistance of a number of collaborators, has been interested in the subject, and it is proposed to sketch briefly in this paper some of the investigations carried out by him more or less jointly in the pharmacological and psychological laboratories of this university.

I. A QUANTITATIVE STUDY OF ANALGESIA PRODUCED BY OPIUM ALKALOIDS

Opium and some of its alkaloids find their most extensive application in therapeutics in the relief of pain. The comparative efficiency of morphin, codein, papaverin and opium itself in respect to their analgesic powers has, however, never been experimentally investigated, and all our knowledge on the subject has been derived from clinical data. It is, therefore, not surprising to find a great diversity of opinion among various authors in regard to the pain-relieving properties of these drugs. Thus, Claude Bernard [8] regarded narcein, an inert substance according to the majority of investigators, as a powerful narcotic; again, Fronmüller [9] ranked narcotin in activity as next to morphin; while Baxt [10] extolled the wonderful pain-relieving virtues of papaverin. In conjunction with Drs. N. B. Herman and Charles S. Levy the author undertook an investigation of the comparative value of the above drugs by studying their effect upon the sensory threshold for pain on various parts of the skin and mucous membranes.

In our experiments we have made use of a large Baltzer inductorium for producing quickly and conveniently finely graded pain stimuli. Having standardized our apparatus with the help of Dr. C. W. Hewlett, of the Physical Laboratory of this university, we were able to express the values of these stimuli, quantitatively, in henries or C. G. S. units, and in this way compare the strengths of the stimuli required to produce pain under various conditions.

The first step in the investigation was to determine whether a sufficiently constant pain threshold could be established. Martin [11] and his co-workers have studied the threshold of electrocutaneous sensation with the induction current, by dipping a finger in a liquid electrode, and have found that a definite sensory threshold can be established, subject to physiological, diurnal, nocturnal, and fatigue variations. Furthermore, Martin, Grace and McGuire [12], in the only pharmacological study by this method, have found a definite lowering of the sensory threshold after the administration of acetphenetidin by mouth.

In our work we have made use of fine platinum electrodes, studying the effect of the induced current on individual pain points or groups of pain points in four different regions of the body. In this way our chances of error were lowered fourfold. The points most convenient for study employed by us were the skin on the back of the hand between thumb and forefinger, the tip of the nose, the tip of the tongue, and the lips.

In complete agreement with the localization of pain points on the surface of the body, as described by von Frey [13] and others, we have found that at any given spot of the body a definite pain sensation can be elicited by changes in mutual inductance of sufficient intensity, and that for every group of pain-points a pain sensation of exactly the same quality and intensity can be elicited by exactly the same intensity of electrical stimulus. By practice we were able to distinguish changes in pain sensation produced by moving the secondary towards or away from the primary coil a distance of not more than 0.1 cm.

Through numerous observations it was established that the normal pain threshold remains surprisingly constant for many hours in succession, and, through a series of other experiments, lasting over 25 hours each, the diurnal and nocturnal variations were found to be very slight.

Having determined the normal pain threshold in any given experiment, a drug was administered by subcutaneous or intramuscular injection, and after its absorption repeated readings were made. In this way a rise or fall in the pain threshold, or an analgesic or hyperalgesic effect, respectively, was detected and measured.

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Being fully aware of the fact that certain subjective elements, inherent in the character of the investigation, entered into our experiments, we have taken all possible precautions to eliminate errors arising from this source, and have made numerous control experiments.

Each experiment was carried out in the same room, and under perfectly constant conditions. Readings were always taken with the subject in the same position, and the subject was never allowed to look at the apparatus, but sat either with the eyes closed or fixed on some distant point. The electrodes employed were of course the same in any one experiment; the distance between the electrodes was kept fixed; the pressure with which they were applied to the surfaces was kept constant; the direction of their application was the same; and the wetness of the surfaces stimulated was maintained the same as nearly as could be judged.

When a drug was administered the subject was ignorant of its nature. Furthermore, as controls, normal saline and other inactive substances were often substituted in place of the drug without the subject's knowledge. It may be remarked in passing that, owing to the conflicting experiences of previous observers, we could not know the true pharmacological action of most of the alkaloids studied, thus further eliminating any subjective bias.

Action of Opium Alkaloids Individually.—By the above methods the six principal opium alkaloids, morphin, papaverin, codein, narcotin, narcein and thebain were studied. Administered in moderate therapeutic doses, it was found that in respect to their analgesic power, beginning with the strongest and ending with the weakest, they ranged themselves in the following order: Morphin (10 mgs.) → papaverin (40 mgs.) ← codein (20 mgs.) → narcotin (30 mgs.) → narcein (10 mgs.) → thebain (10 mgs.).

In respect to morphin in one of us an idiosyncrasy was noted. The subject (N. B. H.) was rendered hypersensitive to pain, and this effect could be measured quantitatively. This was an interesting confirmation of the existence of undoubted cases of persons who are not relieved by morphin but are rendered even more sensitive by it.

Action of Combinations of Alkaloids.—After a study of the individual alkaloids, the action of combinations of morphin and narcotin meconates (narcophin) and other salts was studied. It was found that a given dose of narcophin has greater analgesic power than is represented by the arithmetical sum of the effect of its constituents, morphin and narcotin. Thus, 5 mgs. of narcophin produces distinct analgesia, while 5 mgs. of morphin alone, or 10 mgs. of narcotin alone, produces no such effect. This observation is in complete agreement with Straub's [14] views on the synergism of these two substances. A similar action was observed with a mixture of the total opium alkaloids (pantopon.) The full data appear in the *Journal of Pharmacology and Experimental Therapeutics*, 1916, VIII, 1.

II. Concerning the Peripheral Action of Opium Alkaloids

As a rule the analgesia produced by opium is, of course, of cerebral origin. Yet, we find a number of opium preparations, such as lotions, plasters, ointments, and suppositories, employed widely by clinicians for what is intended to be a local effect, and indeed some of these preparations are official in the U. S. P. and other pharmacopeias. While the opinion of many clinicians is that opium applied in this way exerts some local action without being absorbed into the system, the majority of modern pharmacologists ridicule this idea, and some go so far as to characterize this practice as a "pharmacological superstition." [15]

If we turn from mere belief or disbelief and speculation to scientific inquiry and experimental evidence on the subject, we find surprisingly few data upon which to base a rational and unbiased opinion. Indeed the few experimental data at our disposal do not at all disparage the local use of the drug.

It is well known, for instance, that dionin or ethyl morphin is a powerful anesthetic and has been used as such in ophthalmic surgery [16]; the same is true of benzoyl morphin or peronin. Moukhtar [17], in an interesting experimental work on guinea-pigs, found that intradermal injections of minute quantities of solutions of opium alkaloids show a distinct local effect on the sensory nerve terminals, an effect which is not due to mechanical distension of tissue, as he proved by control injections of physiological saline solution. Even more interesting is the accidental discovery by Pal [18] of the locally anesthetic action of papaverin. On tasting a little papaverin sulphate he noted a numbness of the tongue. Further investigation by him showed that the alkaloid possesses marked local anesthetic properties, so that on applying it to a rabbit's eye a painless operation could be performed.

In order to clear up this perplexing question, experiments were carried out by the author in conjunction with Drs. H. J. Bollinger and S. L. Johnson. The method was the same as that employed in the previous research. The normal sensory threshold for pain on various parts of the skin and mucous membranes was determined by the electrocutaneous method. Various opium alkaloids were then applied locally for different periods of time, and the pain threshold was again determined.

It was found that the various opium alkaloids, when applied locally to the skin or mucous membranes, exert a distinct effect upon the sensory nerve endings, raising the sensory threshold as indicated by the greater amount of electrical stimulation required to produce the first sensation of pain. The most efficient in this respect was papaverin; next in order was narcotin; third came morphin; with narcein, codein, and thebain following in the order of their efficiency.

It was furthermore noted that a mixture of the total opium alkaloids (pantopon) exerted this effect even in a greater degree than the amount of morphin or papaverin which it contains would do if applied alone. From this it follows that the different alkaloids seem to potentiate each other, just as they

do when injected subcutaneously or intravenously and absorbed by the blood.

Without presuming to magnify its importance, it is evident, therefore, that opium, although primarily a central nervous poison, does also act to some extent upon peripheral structures, *i. e.*, sensory nerve endings, and that the empirical observations of the older clinicians, who advocated local applications of opiates for the relief of pain, are not totally without foundation. This would seem to be the more plausible if we bear in mind that in our experiments the time of application was purposely made as short as possible (generally from one to five minutes) on the one hand, while, on the other hand, the opium applications employed in clinical practice were allowed to remain in contact with the skin or mucous membranes over long periods of time. The complete data appear in the *Journal of Pharmacology and Experimental Therapeutics*, 1916, VIII, No. 8, August.

III. Analgesia after Antipyretics

Inasmuch as the so-called antipyretic drugs produce also a distinct relief of pain in many conditions especially of a neuralgic character, it was interesting to inquire into their comparative efficiency. Accordingly, experiments were performed with the view of determining the pain threshold before and after administration of such drugs, in exactly the same way as had been done in the case of the opium alkaloids. This investigation has not yet been completed, but the author may say in this place that here too a lowering of the pain threshold was observed. Several antipyretics were studied and all of them were administered by mouth. It was found that acetanilid, acetphenetidin and pyramidon were especially effective in this respect. The results so far obtained indicate that the antipyretics, while not as powerful as the opiates, do also produce analgesia of the central origin, as shown by the change in the pain threshold after their administration.

IV. Action of Opium Alkaloids on Psychological Reaction Time

Following the studies on analgesia, an attempt was made to learn more about the effects of morphin and opium on the higher intellectual centers of the brain by means of observations on the reaction time before and after administration of those drugs. This investigation was conducted by the author, together with Captain S. Isaacs.

The experiments were made on the authors themselves and on ten colleagues, making twelve normal subjects in all.

The reaction time was measured by means of an improved chronoscope devised by Prof. Knight Dunlap, which is a far more accurate and convenient instrument than the old Hipp instrument. The apparatus is described by Professor Dunlap elsewhere.[19] It consists essentially of a synchronous motor, run on a tuning-fork vibrating fifty times per second, and registering the time in units of 2σ or 1/500 of a second, the dial-hand of the chronoscope being controlled by an electromagnetic clutch.

The simple sound reaction was obtained by the experimenter calling out a word or number into the speaking disc which started the chronoscope and the subject responding with a set answer as soon as possible through another speaking disc, thus stopping the clock. The results were then recorded in terms of 2σ or 1/500 of a second. It is needless to state that the subject and experimenter were separated by a curtain in order to prevent their seeing each other.

The simple touch reaction was obtained in a similar manner. The experimenter touched the hand of the subject behind a curtain, the pressure of the touch starting the chronoscope going. The subject responded as soon as he perceived the touch sensation by pressing a bulb or touching a key which immediately stopped the clock.

The simple light reflex was tested by the experimenter pressing a key and thus lighting an incandescent lamp behind a white screen, the subject responding by pressing another key which extinguished the light and stopped the chronoscope.

In order to determine the more complex reaction time or association reaction time, various devices were tried, such as response to certain words (noun and adjective, subject and predicate, etc.), but none of those were found satisfactory for the purpose in view. The most convenient and satisfactory method was finally found to be the calculation of a mathematical problem. Two sets of problems were submitted to the subjects in all experiments. In one series the subject was requested to add 17 mentally to a two-figure number, and announce the sum as quickly as possible through a telephone arrangement which breaks the circuit and stops the clock. In the second series a more difficult task was given to the subject. The experimenter in this case announced a two-figure number and the subject was required to multiply the same by 3 and add 4 to the product, and then announce the result through the speaking disc, thus recording the reaction time.

In each test twenty numbers were generally employed at each sitting. This method furnished quite a complicated association test and at the same time eliminated as much as possible memory and habituation or familiarity. The subject in every case was expected to go through the mathematical process in his mind and not rely on his memory at all. Great attention was paid in the association tests to the number of errors made, and these were recorded for comparison of the normal reaction time with that obtained after the administration of the drug.

After the normal simple and complex reaction times had been established in any one experiment, the subject was given a drug by subcutaneous injection. The reaction times were then again measured in several series and the results tabulated and analyzed.

In testing simple reactions to sound, touch and light, the number of readings taken was generally from twenty to fifty or more in each series. In testing the association time, twenty problems were submitted by each method. An average reading was computed with the help of a calculating machine, thus saving an enormous amount of time, and the mean variations

were also computed by means of an adding machine, in accordance with Dunlap's method.[20]

Control experiments were occasionally made with injections of physiological saline solution, while the subject was under the impression that he was receiving a drug. It may be here stated that in such cases no definite change in the reaction time was noted.

It was found that the effect of a morphin injection depends on the size of the dose and manifests itself in one or more of three ways. In the first place, the absolute reading of the reaction may be affected. In the second place, the mean variations in the readings may be greatly increased or decreased In the third place, in the case of association reactions, there may be an effect noted on the accuracy with which the subject performs mental problems.

After small doses of morphin (4-6 mgm.) there was noted a distinct *primary effect,* which consisted in a stimulation or a shortening of the reaction time, or in a decrease in the mean variation of the readings, or sometimes in both, and furthermore, in a lesser number of errors made in the computation of mathematical problems. This primary effect of morphin generally lasted half an hour or more and was followed by a secondary stage characterized by a depression, as indicated by the prolongation of the reaction time and greater variations in the readings or both. After very small doses of morphin, however, the depression was sometimes lacking.

After larger doses of morphin (8 to 15 mgm.), the primary stage of stimulation was very short and could be easily overlooked unless the readings were begun very soon after the injection of the drug. Depression, on the other hand, was the predominant picture, as could be seen by the prolongation of the reaction time readings and greater variations in the same, and also, in case of associations, by a greater number of mistakes.

Although the two stages of morphin action above described were not always marked, a careful analysis of all the experiments indicated that they were present in almost all the cases. The primary stage of quickening or stimulation, in our opinion, probably corresponds to the stage of *euphoria* or well-being so well known to the pharmacologist and which occurs after small doses of opiates. It is this euphoria or sense of well-being which probably is responsible in a great measure for the greater accuracy in mathematical calculations, especially in subject with a nervous temperament, inasmuch as the narcotic action of the drug is just sufficient to "take the edge off" the subject's anxiety. The primary stage of increased efficiency noted agrees well with the results of some other tests of mental efficiency produced by opium by mouth described by Münsterberg.

Three experiments were made with injections of narcotin hydrochloride alone. No definite change in the reaction time was produced by that drug.

Three experiments were made with a combination of morphin and narcotin in the ratio of one to two, by administering the drug called narcophin, which is a mixture of morphin and narcotin meconates. In two of the experiments there was a definite increase in narcosis and corresponding prolongation or depression of the reaction time noted as compared with morphin alone, being very marked in one case, but of a lesser degree in the other. In the third case the narcosis was, if anything, less than that produced by morphin alone.

Seven experiments were made with a combination of all the opium alkaloids in the form of pantopon, a mixture of hydrochlorides containing 50 per cent of morphin. In four of the experiments there was a very marked increase in narcosis and prolongation of the reaction time produced by pantopon as compared with that produced by the same amount of morphin when given alone The deeper narcosis in these cases was also shown by the greater number of errors in the association problems. In two other cases the deeper narcosis was also present, but not in so marked degree as in the preceding two, and in one experiment the result was doubtful.

On analyzing all the experiments with pantopon and narcophin, the results could be summarized as follows: Out of ten experiments five showed a marked increase in narcosis and prolongation of the reaction time; three experiments showed also a definite but not so marked a prolongation of the reaction time as compared with morphin alone; one subject gave doubtful results, although his accuracy was markedly affected in regard to association problems, and in one case the reaction time was quickened by the combination more than it was by morphin alone. It was also noted that in all experiments, both with morphin alone and with its combinations, the simple reactions were less affected by the drugs than the association tests, thus showing that the narcotics exerted their influence especially upon the higher functions of the brain. The complete data appear in *Psychobiology,* 1918, I, 327.

V. Effect of Some Antipyretics on Reaction Time

Having studied the effects of opium and morphin on simple and complex reaction times, it was interesting to inquire into the effect of the other great class of analgesic drugs, the antipyretics, on the same functions. Precisely the same method was employed in this research which was performed by the author in collaboration with Messrs. S. Isaacs and J. Greenberg. In this set of experiments, however, the drugs were given by mouth.

The experiments were performed for the most part on the authors themselves, and occasionally on other subjects. About forty experiments were made in all, each lasting from two to five or more hours. The drugs studied were the following: quinin, acetanilid, acetphenitidin (phenacetin), antipyrin, phenyl salicylate (salol), acetylsalicylic acid (aspirin), and pyramidon. In order to ascertain whether these drugs produced a synergistic effect or not, the following combinations were also studied: acetanilid and salol, phenacetin and salol, acetanilid and phenacetin, aspirin and salol, and antipyrin and aspirin. The doses of the drugs never exceeded those employed by conservative therapeutists.

A careful study and analysis of all the data obtained has led the authors to the following conclusions. The results obtained with antipyretics are quite different from those found after morphin or opium. No primary stage of stimulation or shortened reaction time was noted after administration of antipyretics, except possibly after small doses of quinin. It was found that in all cases the ordinary doses of antipyretics produced either very little effect on the reaction time, or if affecting it at all, they always impaired it as indicated by the prolongation of the mean readings, by the increase in the mean variations of readings, or by both. The most powerful or depressant drug in this respect was found to be pyramidon. This is not surprising, inasmuch as pyramidon in the author's (M.) experience and in the experience of many physicians is one of the most efficient analgesics—its effect coming closer to that of the narcotics than that of most other antipyretics. It was furthermore interesting to note that when the antipyretics exerted an influence on the reaction time, the simple reflexes or reactions to sound, light and touch were more prolonged or impaired that the more complex association tests. Of the three simple reactions that of touch was more generally retarded than those of sound or light. The association tests were also depressed or impaired, but usually in a distinctly lesser degree than the simple reactions or reflexes. Thus, for instance, the absolute readings in case of the mathematical calculations were sometimes even actually improved and the depressant effect of the drug revealed itself only through the greater numbers of errors committed.

Experiments with combinations of the various antipyretics gave results which could be explained by a simple summation or addition of the individual effects of the components. No so-called synergism or potentiation of one drug by another was observed.

The curious difference in the effect of the drugs on the simple reactions as compared with that on the more complex ones is the direct opposite of the results obtained after adminisration of opium or morphin. In the latter case, the simple reactions were always less impaired than the more complex association tests. A comparison of the findings obtained with the two groups of analgesics, the opiates or narcotics, and the antipyretic analgesics, seems to point to some lower synapse as the seat of action of the coal-tar derivatives. The full data appear in *Psychobiology*, 1917, I, 19.

VI. Effect of Antipyretics on the Neuromuscular Test of "Tapping"

This test consists briefly in the continuous tapping by the subject with a brass stylus upon a brass plate so adjusted that each tap or contact of the stylus on the brass plate is electrically registered on a counter. The number of taps made over a definite period of time is a rough index of the neuromuscular coördination of the muscles of the arm and hand. In the present investigation, observations were made upon the authors and occasionally on other subjects. The subject was required to tap continuously for three minutes at a time, and the number of taps registered was noted at the end of each minute. Having noted the normal tapping in any one experiment, the subject was given an antipyretic by mouth and the test was repeated, generally about an hour later, but in some cases several readings were repeatedly taken at definite intervals. The effect of the following drugs was studied: Phenacetin, antipyrin, acetanilid, quinin sulphate, pyramidon, aspirin and salol. In addition to the study of individual drugs, the following combinations were also administered: Acetanilid plus phenacetin, 5 grains each; phenacetin plus salol, 2½ grains each and 5 grains each; aspirin and salol, 5 grains each; acetanilid and salol, 2½ grains each and 5 grains each and antipyrin and aspirin, 5 grains each. The results of the experiments were not very striking. Briefly, however, the effects of the drugs may be summarized as follows: Phenacetin, acetanilid, antipyrin and quinin in the ordinary doses (not exceeding 5 grains) showed a definite tendency to improve the tapping rate. Larger doses of these drugs (8 or more grains) tended to impair the efficiency in the test. The improvement after phenacetin and antipyrin was greater than that after acetanilid and quinin. After pyramidon, salol and aspirin, no definite change could be noted as the different subjects showed different results. Combinations of the various drugs studied all showed a tendency to improve the tapping rate. This was especially marked after the combinations of acetanilid and salol and phenacetin and salol. (See *Proceedings of Society for Experimental Biology and Medicine*, 1917, XV, 61-62.)

This investigation as well as the following was conducted by Drs. Macht, Isaacs and Greenberg.

VII. Effect of Opiates and Antipyretics on the Field of Vision

The same experimenters studied the influence of some opiates and antipyretics on the field of vision. Observations were made on the authors themselves and some of their colleagues with an ordinary perimeter, the field of vision being tested for four colors, white, blue, red and green.

It was found that the opiates, morphin and pantopon, taken by injection in every case produced a definite though very slight contraction of the field of vision. As between morphin and pantopon, little difference was noted, yet it may be well to state that in two out of three subjects, on whom the observations were made, the morphin injections seemed to produce a slightly greater limitation of the field of vision than pantopon.

Of the antipyretics studied it was found that they produced either no change in the field of vision at all or had a slight tendency to increase it. This was especially noted in the case of acetanilid, acetphenetidin, aspirin, and the combinations acetanilid plus salol and acetphenetidin plus salol, which in some of the experiments produced a definite though not marked increase in the field of vision. It was curious to note, furthermore, that the increase was especially apt to occur for

the white and blue colors, which ordinarily under normal conditions give the largest field of vision.

The conclusions drawn from all the observations are that the opiates, while producing but little effect upon the field of vision in the normal subject, when they do exert any influence, tend to narrow the field, whereas the antipyretics, when any effect is to be noted, tend to increase the field of vision. What mechanism it is that produces the positive findings in the different cases, it is difficult to say. At any rate, various factors, such as the constriction of the pupil in the case of opium, vasomotor changes produced by antipyretics, specific effects upon the retinal ganglia and nerves and central cerebral effects must be all considered. (See *Proceedings of Society for Experimental Biology and Medicine*, 1917, XV, 47-48.)

VIII. Concerning the Influence of Antipyretics on the Acuity of Hearing

While conducting the above experiments with antipyretics, the authors (Macht, Greenberg and Isaacs) made systematic observations on the effects of these drugs on hearing. The results were very interesting and unexpected. The experiments were performed on normal human subjects and in a few cases on persons suffering with mild deafness. The tests were made by means of a watch, in a quiet room, with the subject in a sitting position; and all necessary controls were carried out for the elimination of errors In every experiment the normal limit of error was first determined; the drug to be studied was then administered by the mouth, and the acuity was afterwards tested at definite intervals of time. Only therapeutic doses of the drugs were administered. The following substances were studied: acetanilid, acetphenetidin, antipyrin, pyramidon, lactophenin, salol, aspirin, quinin, sodium salicylate, and "melubrin." After studying the effects of individual drugs, certain combinations were administered. The following were among the combinations studied: acetanilid plus sodium bicarbonate, acetphenetidin plus salol, acetanilid plus salol, acetnailid plus acetphenetidin, antipyrin plus aspirin, and antipyrin plus salol.

The results obtained were interesting and unexpected. It was found that some drugs decrease the acuity of hearing while others increase it. Furthermore, it was found that certain combinations of antipyretics produce synergistic effects not explainable by the simple arithmetical sum of the effects produced by the components individually. Among the agents found to decrease the acuity of hearing were acetanilid, salol and aspirin. Among those found to increase the hearing were antipyrin, pyramidon, and small doses of quinin. Among the most remarkable combinations studied were those of acetanilid plus sodium bicarbonate and acetanilid plus salol. It was established that whereas acetanilid given alone decreases the acuity of hearing, and ordinary doses of sodium bicarbonate given alone produce no change, a combination of the two produced a definite improvement in the acuity of auditory perception. Again, whereas acetanilid and salol, when administered separately, each by itself tended to impair the hearing, a combination of the two actually increased the acuity of sound perception. The peculiar synergism of acetanilid with sodium bicarbonate recalls the experiments of Hale [1] who called attention to the fact that such a combination is less toxic for animals than the same dose of acetanilid given alone.

Complete data of this research, together with an attempt at an explanation of this peculiar synergism, appear in the *Journal of Pharmacology and Experimental Therapeutics*, 1920, XV, 1.

IX. Effect of Anesthetics on the Subsequent Behavior of Rats

During the past year or two the author, in conjunction with Dr. C. F. Mora, has been conducting psychopharmacological experiments on the behavior of albino rats. These experiments were performed by means of the circular maze, with camera lucida attachment invented by Prof. John B. Watson, of the Psychological Department of this university. In connection with these experiments, the authors are greatly indebted to Professor Watson for the apparatus as well as for valuable advice. The maze has been described by Professor Watson elsewhere.[2] By means of this apparatus one can study the rate of learning in albino rats and the effect of various factors on memory habit after they have learned the maze problem. The present authors studied the effects of various drugs on both of these. The effect of the general anesthetics, chloroform, ether and nitrous oxide, was investigated. It was found that the three anesthetics, chloroform was the most deleterious in its effects and for the subsequent behavior of the animals. The experiments were performed by first training rats so that they found their way through the maze by the shortest route and in the quickest time. After this habit was established the rats were anesthetized and their behavior was again noted, with especial reference to how soon they regained their normal intelligence after the anesthesia was over. It was found that after chloroform the rats were depressed a very long time. Their memory was impaired and it took quite a long time before they regained their previous agility Ether did not produce much depression, unless administered for a very long time, and even after prolonged ether anesthesia the animals recovered more quickly than after chloroform. Nitrous oxide and oxygen anesthesia was the least depressing of the three. (See *Proceedings of Society for Experimental Biology and Medicine*, January, 1920.)

X. Effect of Opiates on the Behavior of Albino Rats

The author and Dr. C. F. Mora have conducted an extensive investigation of the effect of opiates on the behavior of rats in the circular maze. About twenty rats were studied in this research; and the effect of the following drugs was noted: Morphin, codein, papaverin, narcotin, narcein, thebain, pantopon, and narcophin. In this research the effect of the opiate was studied on the behavior of the rats after training in the maze and not on the rate of learning. It was found that morphin, even in minute doses, markedly impaired the mem-

ory-habit and activity of the animals. Codein, in nine experiments out of eleven, produced a depression, and in two experiments, no change. Narcotin, in five experiments out of seven, was depressant, and in two experiments produced little or no change. Narcein, in six experiments out of ten, showed little or no effect, and in four experiments a slight depression. Thebain, in one experiment out of eleven, showed a stimulation, and in ten experiments, a retardation. The least depressant of the individual alkaloids was found to be papaverin, which produced depression only after very large doses, but otherwise had no effect. Out of all the morphin experiments, in one animal a primary excitation was noted after a small dose of the drug. The morphin combinations, pantopon and narcotin, in the majority of the experiments were found to be much less depressant than the corresponding doses of morphin alone in the same animals. It was very interesting to find that in all experiments, even where large doses of the narcotics were administered and produced marked and prolonged depression or impairment of the cerebral functions, the animals sooner or later all recovered their intellectual activities. This, of course, is very encouraging experimental evidence in connection with the clinical treatment of the opium or morphin habit. Full data will appear in the Journal of Pharmacology and Experimental Therapeutics.

REFERENCES

1. Benedict and Dodge: Psychological effects of alcohol. Carnegie Institution of Washington, 1915.
2. Dietl and Vintschgau: Pflüger's Arch., 1871, XVI, 316.
3. Hollingsworth: Arch. of Psychol., No. 22, April, 1912.
4. Loewald: Kraepelin's Psychologische Arbeiten, 1896, I, 489.
5. Poffenberger: Amer. Jour. Psychol., 1914, XXV, 82.
6. Lashley: Psychobiology, 1917, I, 141.
7. Münsterberg: Beiträge zur Exp. Psych., 1892, IV, 121-146.
8. Claude Bernard: Compt. rendus, LIX, 464.
9. Fronmüller: Klinische Studien ueber narcotischen Arzneimittel, Erlangen, 1869.
10. Baxt: Arch. f. Anat. u. Physiol., 1869, p. 112.
11. Martin, Porter and Rice: Psycholog. Review, 1913, XX, 194.
12. Martin, Grace and McGuire: Jour. Pharmacol. and Exp. Ther., 1915, VI.
13. Von Frey: Ber. kön. Sachs. Gesell. f. Wiss., 1894, XLVI, 186 and 283. 1895, XLVII, 166, and Jour. Am. Med. Assn., 1906, XLVII, 695.
14. Straub: Biochem. Ztschr., 1912, XLI, 419.
15. Wood, H. C., Jr.: Jour. Am. Med. Assn., 1916, LXVI, 1072.
16. Gwathmey: Anesthesia, N. Y., 1914, pp. 733 and 802 (with bibliography).
17. Moukhtar, A.: Compt. rendus. Soc. biol., 1909, LXVI, 187.
18. Pal, J.: Deut. med. Wchnschr., 1914, XL, 164.
19. Dunlap: Jour. Exp. Psychol., 1917, II, June.
20. Dunlap: Psycholog. Review, 1913, XX, 154.
21. Hale: U. S. Hygienic Lab. Bull., IV, 53, 1909.
22. Watson, John B.: Journal of Animal Behavior, Jan.-Feb., 1914, 4, No. 1, 56-59.

A BIOLOGICAL STUDY OF HEMOLYTIC STREPTOCOCCI FROM THROATS OF PATIENTS SUFFERING FROM SCARLET FEVER. PRELIMINARY REPORT

By WALTER P. BLISS

(From the Biological Division of the Medical Clinic, The Johns Hopkins University and Hospital)

The relationship of *S. hemolyticus* to scarlet fever has long been the subject of controversy, certain investigators claiming for it an etiological rôle, while others maintain that the streptococcus found is probably a secondary invader, which might possibly be responsible for many of the common complications of scarlet fever, but is not the causative agent. Although *S. hemolyticus* is practically always found in the throats of individuals suffering from scarlet fever, yet marked variations in carbohydrate fermentation reactions and in the ordinary cultural differential tests favor the opinion that the streptococcus in these cases constitutes a heterogeneous group.

The development of a technic for the differentiation of hemolytic streptococci into groups by means of agglutination and protection experiments devised by Dochez, Avery and Lancefield[1] has made it possible to use this technic in the study of a series of strains of streptococcus isolated from the throats of patients with scarlet fever to determine whether or not there is any biological relationship among the organisms studied. A study has been made of 25 strains of *S. hemolyticus* isolated from as many cases of scarlet fever, for the most part during the first week of the disease when the majority of throats showed the hemolytic streptococcus as the predominating organism. Control tests were carried out at the same time with hemolytic streptococci obtained from human sources in other pathological conditions, for example, tonsillitis, abscesses, septicemia, erysipelas. All organisms isolated were Gram positive streptococci of the type of *S. hemolyticus* with individual variations in size, length of chain, degree of hemolysis, morphology of colony and initial growth in broth—differential characteristics emphasized by some of the earlier investigators, but not peculiar to the streptococci of any particular pathological condition.

Agglutination tests were made following the technic of Dochez and Avery. The strains varied greatly in the diffuseness of growth in broth, but it was found that after several transfers in an optimal medium the suspensions usually became perfectly diffuse and were available for agglutination tests. Particular care in the preparation of the broth was necessary: Fresh beef, carefully freed from fat, infused in

[1] Dochez, A. R., Avery, O. T., and Lancefield, R. C., J. Exp. Med., 1919, XXXI, 179.

TABLE I

Scarlatinal streptococcus strains	Antistreptococcic sera								
	Non-scarlatinal					Scarlatinal			
	Type S3	Type S23	Type S32	Type S60	Type S84	Type S273	23	24	25
11	—	—	—	—	—	+++++	++++	+++++	+++++
12	—	—	—	—	—	++++	+++++	++++++	+++++
13	—	—	—	—	++++	++++	++++	+++++	+++
14	—	—	—	—	++++	+++	+++++	++++++	++++
15	—	—	—	—	—	+++++	++++	+++++	+++++
16	—	—	—	—	++++++	+++++	++++++	++++++	++++++
20	—	—	—	—	—	—	—	—	—
23	—	—	—	—	—	++++	++++++	+++	++++++++
24	—	—	—	—	—	++++	+++++	++++++	++++++
25	—	—	—	—	+++++	+++++++	++++++++	+++++	++++++++
26	—	—	—	—	—	—	—	—	—
27	—	—	—	—	—	++++	+++	+++++	++++
28	—	—	—	—	—	++++	++++	++++++	++++++
29	—	—	—	—	—	++++	+++	++++++	++++++++
35	—	—	—	—	—	+++	+++	+++	++
36	—	—	—	—	—	—	—	—	—
38	—	—	—	—	—	+++++	++++	+++++	++++++
39	—	—	—	—	—	+++++	++++	+++++	++++++
45	—	—	—	—	—	—	—	—	—
47	—	—	—	—	++++	+++++	+++	++++++	+++++
50	—	—	—	—	+++++	++++++	++++	++++	++++++
53	—	—	—	—	—	+++++	++++	++++++	+++++
54	++++++	—	—	—	—	—	—	—	—
56	—	—	—	—	—	++++	+++	++++++	+++
S 273	—	—	—	—	—	++++++	+++++	+++	+++++

\+ indicates agglutination present in a dilution of 1:20; ++ 1:40; +++ 1:80; ++++ 1:160; +++++ 1:320; ++++++ 1:640; +++++++ 1:1280; ++++++++ 1:2560. The minus sign (—) indicates no agglutination.

TABLE II

Non-scarlatinal streptococcus strains	Antistreptococcic sera				Non-scarlatinal streptococcus strains	Antistreptococcic sera			
	Non-scarlatinal	Scarlatinal				Non-scarlatinal	Scarlatinal		
	Type S60	Type S273	24	25		Type S60	Type S273	24	25
4	—	—	—	—	32	—	—	++	—
5	—	—	—	—	37	—	—	—	+
6	—	—	—	—	40	—	+	—	—
9	—	—	—	—	41	—	—	—	—
10	—	++++	++++	+++++	49	—	—	—	—
21	—	—	+	—	55	—	+++++	++++	+++++
22	—	—	—	—	57	—	+++++	—	++++
31	—	—	—	—	58	—	—	—	—
					59	—	—	—	—

distilled water, was used, made up in the customary manner, with the addition of dibasic potassium phosphate as buffer, adjusting the reaction to a pH of 7.8 before fractional sterilization in the Arnold, so that the final reading after sterilization was approximately 7.5. Even with this medium it was necessary in the case of certain strains to pass them through several generations in glucose broth in order to get them diffuse, or even through blood or ascitic broth. In the agglutination tests fresh 18- to 24-hour broth cultures were used, 0.3 c. c. to each tube, to which were added equal parts of the serum to be tested in a final dilution of from 1 to 20 to 1 to 640 (in some cases 1 to 2560) with a normal serum control for each dilution and a control in broth set up at the same time. The serum dilutions were made in broth of the same lot as that used for the bacterial suspensions. It was not found necessary to wash and resuspend the cultures as Dochez and Avery recommend. The mixtures were incubated in the water-bath at 56° C. for one hour, after which readings were made.

It will be recalled that in the work of Dochez and Avery, carried out principally with hemolytic streptococci from measles and various respiratory infections, 68 per cent of the strains were differentiated into four definite types: the so-called Type S3, Type S23, Type S60 and Type S84. Subsequently they have added two other groups: Type S32 and Type S273. The type organisms used in making the specific sera for their agglutination tests were obtained from throat cultures from lobar pneumonia (S23), measles (S60), lung cultures from bronchopneumonia (S3 and S32), pleural fluid from bronchopneumonia (S84) and pus from a case of scarlet fever (S273).

In this preliminary series of agglutination experiments 25 hemolytic streptococcus strains of scarlatinal origin have been tested against these six antistreptococcic sera of Dochez and Avery, five of them of non-scarlatinal origin and one (Type S273) of scarlatinal origin, and in addition against three antistreptococcic rabbit sera prepared by immunization with three of the author's strains, namely, Nos. 23, 24 and 25. The condensed results are presented in the accompanying tables.

It will be noted in Table I that all strains isolated from throats of patients with scarlet fever, with the exception of Nos. 20, 26, 36, 45 and 54, were agglutinated by all four antistreptococcic sera made from strains isolated from patients with scarlet fever, in the majority of instances in as high dilution as the homologous strains. Inasmuch as in most cases only one colony was isolated from any particular throat culture, and in view of the fact that more than one strain of hemolytic streptococcus may be present in these throat cultures (as would be suggested by the presence of a Type 3 organism in No. 54 above), the five exceptions just noted may be due to having selected a colony of another type instead of an organism of this particular group. Furthermore, these same 20 strains failed to be agglutinated by any of the five antistreptococcic sera of non-scarlatinal origin, where rabbit sera were used that did not show a tendency to non-specific agglutination of streptococci or where sheep sera were available. However, in the case of serum Type S84, which showed such a tendency to non-specific agglutination with six strains, no sheep serum has as yet been available.

In Table II it is seen that but three (Nos. 10, 55 and 57) of the 17 *S. hemolyticus* strains from sources other than scarlet fever were agglutinated by the three sera of scarlatinal origin used. These three deserve special consideration. No. 10 was from a case of acute tonsillitis in a patient who had been exposed to scarlet fever, but who did not develop an exanthem.

No. 55 was isolated from the pus from a mastoid during operation on a nurse who had entered the hospital one week previously with a severe sore throat, aching, general malaise, fever, followed by an acute suppurative otitis media and then an acute mastoiditis. This strain was found in pure culture in the pus from the mastoid at the time of operation and subcultures were agglutinated by the three antistreptococcic sera of scarlatinal origin. Three days after operation redness appeared about the site of the operating wound, which in the next 24 hours had spread over the entire face, neck, shoulders, axillæ, both arms, chest, back, abdomen, perineum and thighs, and then more slowly spread down to the ankles. The condition was diagnosed as erysipelas. Two weeks later extensive desquamation started, which has continued to date.

No. 57 was admitted to the isolation ward as a suspected case of scarlatina, at about the same time that several other nurses had developed scarlet fever. The patient was suffering with a severe sore throat, characterized by redness and swelling of tonsils and pharynx, without membrane formation, and with marked swelling and tenderness of the anterior cervical lymph glands, flushing of the face, neck and chest, but no generalized erythema.

One other fact was of some interest. All 25 streptococcus strains from patients with scarlet fever fermented both lactose and salicin (except Strain 36), 5 of the 25 also fermenting mannit, thus placing them in Holman's classes of *S. pyogenes* (20 strains) and *S. infrequens* (5 strains) respectively, and not in the group of *S. anginosus* where Holman placed most of his strains from various throat infections, including scarlet fever. This work would indicate, therefore, that the streptococci found in throat cultures in cases of scarlet fever do not fall in the anginosus group, but in the majority of instances in the pyogenes group.

CONCLUSIONS

1. In a study of 25 strains of *S. hemolyticus* isolated from the throats of patients with scarlet fever, 20 or 80 per cent were agglutinated by four different antistreptococcic sera made with streptococci isolated from scarlet fever cases.

2. None of these strains were agglutinated by five antistreptococcic sera of non-scarlatinal origin (except in the few instances noted).

3. But three of seventeen strains of non-scarlatinal origin were agglutinated by these three sera of scarlatinal origin, and

these three may have been either atypical scarlatinas or scarlatinal contacts.

4. Certain differences in cultural characteristics, particularly in the fermentation of carbohydrates, were noted.

From this study, therefore, it would appear that a great majority (80 per cent) of strains of *S. hemolyticus* isolated from the throats of patients with scarlet fever belong to a specific biological type as determined by the reaction of agglutination. It is possible that the heterogeneous strains found may be accidental dwellers in the throat and that a more careful selection of colonies may reveal a still higher proportion of unit type organisms.

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